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

HEALTH TECHNOLOGY ASSESSMENT

Braftovi

50 mg capsule, hard x 28

75 mg capsule, hard x 42

INN Encorafenib

Therapeutic indication(s)	In combination with binimetinib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
Start/end date of procedure	07.04.2021 – 20.12.2021
Final decision	Inclusion in Annex 2 of the Positive Drug List (PDL) for purchase by the healthcare facilities with state and/or municipality ownership and under Article 5 of the Medical Establishments Act, and reimbursement by the NHIF beyond the value of the provided medical services.

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

Health problem

Melanoma is an aggressive form of skin cancer with an increasing incidence worldwide and a high associated mortality rate, making it a significant public health concern. Several risk factors for cutaneous melanoma have been identified, with the complex interaction between various genetic and environmental factors playing a critical role.

The diagnosis of melanoma is typically confirmed through dermoscopy, biopsy, and histopathological examination, which should adhere to the American Joint Committee on Cancer (AJCC) classification and include information on maximum thickness (Breslow), mitotic rate, presence of ulceration, degree of regression, and the anatomic location and extent of sun damage, as well as the melanoma subtype. Mutation testing for actionable mutations is essential for patients with advanced disease.

Malignant melanoma is a type of skin cancer that arises from the malignant transformation of melanocytes (the cells that produce melanin), with approximately 90% of melanomas originating in the skin. Although it accounts for less than 5% of all skin cancers, malignant melanoma is the most aggressive form of skin cancer and can be fatal, particularly if not diagnosed and treated in its early stages. Melanoma typically progresses slowly but steadily from benign melanocytic nevi to metastatic melanoma. Most nevi are benign melanocytic neoplasms found on the skin of most individuals, arising from the controlled proliferation of normal melanocytes. Melanoma develops from pre-existing nevi in about 20-40% of cases, while the remaining cases occur de novo.

BRAF mutations are observed in up to 70% of melanoma patients, with the V600E variant being the most common (present in up to 90% of BRAF V600 mutation-positive melanomas) and approximately 50% of cases of advanced disease. This mutation leads to the activation of abnormal pathways and uncontrolled cell proliferation (i.e., cancer). BRAF mutations are associated with a younger age of onset and intermittently sun-exposed skin.

Epidemiological Data

Melanoma is a critical public health problem with an increasing incidence of the disease and associated high mortality. Frequency of BRAF V600 mutations in patients with metastatic melanoma ranges from 40 to 60% in Europe. Currently there are no epidemiological data for Bulgaria.

Efficacy data

The key evidence for the clinical efficacy, safety, and tolerability of Encorafenib in combination with Binimetinib was evaluated in a randomized (1:1:1), active-controlled, open-label, multicenter, Phase III COLUMBUS trial conducted in two parts. The trial involved patients with unresectable or metastatic melanoma with a BRAF V600E or K mutation, confirmed through BRAF testing.

COLUMBUS Part 1:

- **Trial Design**: The first part of the COLUMBUS trial provided evidence for the clinical efficacy, safety, and tolerability of Encorafenib 450 mg once daily combined with Binimetinib 45 mg twice daily (referred to as Combo 450). This was compared against monotherapy with Vemurafenib 960 mg twice daily (which was the standard treatment at the start of the COLUMBUS trial) and Encorafenib 300 mg once daily monotherapy in patients with locally advanced unresectable or metastatic BRAF V600 mutation-positive melanoma. The trial was conducted in 162 clinical centers across 28 countries, with a total of 577 patients randomized equally into the three treatment arms. Patients continued treatment until unacceptable toxicity or disease progression occurred.
- **Primary Endpoint (Efficacy)**: The primary efficacy endpoint was progression-free survival (PFS). The median PFS was doubled with Combo 450 compared to Vemurafenib (14.9 months versus 7.3 months), providing statistically and clinically significant improvement in PFS.
- **Secondary Endpoints (Efficacy)**:
  - **Overall Survival (OS)**: The median OS was more than doubled with Combo 450 compared to Vemurafenib (33.6 months versus 16.9 months).
  - **Objective Response Rate (ORR)**: The ORR was higher with Combo 450 at 63.5% compared to 40.8% for Vemurafenib.
  - **Duration of Response (DoR)**: Responses to Combo 450 were generally durable, with a median DoR of 16.2 months, compared to 7.7 months for Vemurafenib.
  - **Disease Control Rate (DCR)**: DCR was 92.2% in the Combo 450 group compared to 84.0% in the Encorafenib group and 81.2% in the Vemurafenib group.

COLUMBUS Part 2:

- **Objective and Design**: The second part of the COLUMBUS trial was designed according to the FDA's recommendations to further determine the contribution of Binimetinib to the combination with Encorafenib. In this part, a lower dose of Encorafenib (Combo 300) was used to isolate the effect of Binimetinib while keeping Encorafenib exposure comparable to that in the Encorafenib monotherapy arm (also dosed at 300 mg daily). Safety assessments of Combo 450 compared to Encorafenib 300 mg once daily monotherapy were

also included. This part was conducted in 174 clinical centers across 29 countries, with 344 participants enrolled.

- **Results**:
  - **PFS**: The median PFS was 12.9 months in the Combo 300 arm versus 9.2 months in the Encorafenib arm (combining parts 1 and 2).
  - **ORR**: The confirmed ORR was 65.9% for Combo 300 compared to 50.4% for Encorafenib.
  - These results indicated that the combination of lower doses of Encorafenib and Binimetinib (Combo 300) also led to a durable response in patients.

LOGIC Trial (Phase II):

- **Objective and Design**: The LOGIC Phase II trial was a multicenter, open-label trial evaluating sequential treatment with Encorafenib, followed by a rational combination with targeted agents after progression to overcome resistance in adult patients with locally advanced or metastatic BRAF V600 mutation-positive melanoma. The trial was conducted in 22 clinical centers, with a total of 158 patients included.

Conclusion: The COLUMBUS trial provides robust evidence that the combination of Encorafenib and Binimetinib significantly improves progression-free survival, overall survival, and objective response rates compared to Vemurafenib monotherapy in patients with BRAF V600E/K mutation-positive melanoma. These findings strongly support the clinical use of this combination therapy in this patient population.

Safety data

The safety of Encorafenib (450 mg orally once daily) in combination with Vinimetinib (45 mg orally twice daily) was evaluated in 274 patients with unresectable or metastatic melanoma with BRAF V600 mutation (collective population of Combo 450) based on two phase II trials and one phase III trial. At the recommended dose most common adverse drug reactions (ADRs) (>25%), occurred in patients treated with Encorafenib co-administered with Vinimetinib, are: fatigue, nausea, diarrhea, vomiting, retinal detachment, abdominal pain, arthralgia, increased concentration of creatine phosphokinase in the blood and myalgia. The safety of Encorafenib (300 mg orally once daily) in combination with Vinimetinib (45 mg orally twice daily) was evaluated in 257 patients with unresectable or metastatic melanoma with BRAF V600 mutation (Combo 300 population) based on phase III trials. The most common ADRs (>25%) occurred in patients who were treated with Encorafenib 300 mg given together with Vinimetinib were: fatigue, nausea and diarrhea. The safety profile of Encorafenib as a single agent (300 mg orally once daily) is based on data from 217 patients with unresectable or metastatic melanoma with a BRAF V600 mutation (encorafenib pool 300).
The most common ADRs (>25%) reported with encorafenib 300 were hyperkeratosis, alopecia, PRES, fatigue, rash, arthralgia, dry skin, nausea, myalgia, headache, vomiting and itching.

Data on comparators

When choosing BRAF-targeted therapy in the treatment of unresectable or metastatic BRAF V600 positive melanoma, as a comparative alternative to Encorafenib in combination with Binimetinib can be taken with other BRAF inhibitors in monotherapy (Dabrafenib and Vemurafenib) or in combination with MEK inhibitors (Dabrafenib + Trametinib and Vemurafenib + Cobimetinib).

Pharmacoeconomic indicators

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

Binimetinib (in combination with Encorafenib) has also undergone an evaluation procedure of health technology in Great Britain, France, Germany and Sweden and has a positive assessment by each of the HTA agencies of these countries.

Applied analysis
The applied analysis uses cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) methodologies. The objective of the analysis is to evaluate the value-for-money of Binimetinib in combination with Encorafenib for treating patients with unresectable or metastatic melanoma with a BRAF V600E mutation. The comparative alternatives included in the analysis are: BRAF inhibitor monotherapies (dabrafenib or vemurafenib) and combined BRAF and MEK inhibitor therapies (dabrafenib + trametinib and vemurafenib + cobimetinib).

Perspective of the analysis:
- The analysis perspective is that of the payer institution – National Health Insurance Fund (NHIF).
- The time horizon of the analysis is lifetime (30 years).
- The outcome measures used are:
  - For cost-effectiveness analysis: life years gained (LYs).
  - For cost-utility analysis: quality-adjusted life years (QALYs).
- Health benefits and costs are discounted at an annual discount rate of 3.5%.

Survival model:
- The model used for cost-effectiveness modeling includes three mutually exclusive health states:
  - "No progression"
  - "Post-progression"
  - "Death"

Results of the analysis:

- The combination of **Binimetinib + Encorafenib** is associated with more LYs and QALYs compared to all comparative alternatives and incurs lower treatment costs compared to **vemurafenib + cobimetinib**, where it is the dominant alternative.
- The unfavorable values of ICER (incremental cost-effectiveness ratio) and ICUR (incremental cost-utility ratio) compared to monotherapies are due to the higher costs of the combination therapy, which is expected given the use of two drugs, despite its 40% to 50% higher effectiveness as measured by LYs and QALYs.
- The combined therapy with BRAF/MEK inhibitors is preferred over monotherapies due to the significant increase in effectiveness. Therefore, the combined therapies (vemurafenib + cobimetinib and trametinib + dabrafenib) are considered the most relevant comparators from the payer's perspective.
- Among these, **Binimetinib + Encorafenib** is a dominant alternative compared to **vemurafenib + cobimetinib** and a cost-effective alternative compared to **trametinib + dabrafenib**.

Subgroup analyses
Not applied.

Costs for the assessed health technology
The model includes the health technology costs, costs of comparative alternatives, costs of follow-up therapy, costs of medical services.

Budget impact analysis
The budget impact analysis (BIA) was conducted from the perspective of the paying institution – the National Health Insurance Fund (NHIF). The time horizon of the BIA covers a period of five years.

Projected patient numbers:

- **First Year:** 14 patients
- **Fifth Year:** 41 patients

results:

- The introduction of the new health technology will lead to additional costs for the paying institution over the entire time period of the analysis.
- Risk-sharing agreements and patient access schemes were not considered in the analysis.

Conclusion

Melanoma is a significant public health problem with increasing incidence of the disease and associated high mortality. Given the high unsatisfied needs in patients with unresectable or

metastatic melanoma with a BRAF V600 mutation, it is important for clinicians to have more choices when prescribing a targeted combined therapy. Binimetinib in combination with Encorafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation who offers more durable and potent BRAF inhibition with an improved safety profile and tolerance compared to available BRAFi. The introduction of the new health technology will result in an additional cost to the paying institution for the whole considered time period of the analysis, but is also associated with more LYs gained and QALYs relative to all comparative alternatives in the analysis.