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

HEALTH TECHNOLOGY ASSESSMENT

COTELLIC

20 mg film-coated tablets x 63 (3 x 21)

Cobimetinib

Therapeutic indications	In combination with vemurafenib for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.
Start - end of the procedure	17.05.2019 г. – 27.09.2019
Final decision	Final decision is positive for an inclusion in Annex 2 for purchase by medical establishments with state and/or municipal participation and under Art. 5 of the Medical Establishments Act of the Positive Drug List (PDL) and paid by the National Health Insurance Fund (NHIF) beyond the value of the provided medical services.

Summary of the report on the clinical and pharmacoeconomic evaluation of the health technology of the medicinal product Cotellic

Health problem

Melanoma is a malignant, aggressive disease with high growth potential and a tendency to metastasize. The disease is due to the abnormal growth of cells called melanocytes, which are responsible for the production of the pigment melanin. Metastatic melanoma is an advanced form of the disease in which it metastasizes to other parts of the body. This most commonly occurs in the lymph nodes, lungs, liver, bones, brain and abdominal cavity.
Cutaneous melanoma accounts for less than 5% of all skin cancers, but causes 90% of all skin cancer-related deaths. Over 95% of melanomas develop on the skin, but can affect the eyes (uveal melanoma), the lining of the sinuses, the nasal cavity, the oral cavity (mucosal melanoma).
Different instrumental approaches are used to diagnose the disease: assessment by ABCDE rule; dermatoscopy; imaging studies; morphological examinations; genetic research. At present, genetic testing is essential to determine the appropriate therapeutic strategy. The study for the presence of genetic changes - mutations, is mandatory for patients with advanced disease (unresectable stage III and stage IV), and is highly recommended for high-risk disease stage IIc, IIIb-IIIc). The prevalence of BRAF-positive tumors in patients with advanced, unresectable or metastatic cutaneous melanoma reached 45.6%. Melanoma of the skin is most commonly diagnosed in patients aged 65-74 years. The median age of patients at diagnosis was 65 years. The highest mortality rate was in patients aged 75-84 years.

Epidemiological data

Data on morbidity and mortality worldwide according to GLOBOCAN are presented, as well as data for Bulgaria according to the National Cancer Registry. GLOBOCAN data for 2018 show an estimated number of newly diagnosed 287,723 cases of cutaneous melanoma (1.6% of newly diagnosed cancers) worldwide, and an estimated number of deaths of 60,712 (0.64% of deaths from cancer). In Europe, the estimated number of newly diagnosed cases for 2018 is 144.2 thousand (3.7% of newly diagnosed cancers), and the estimated number of deaths - 27.1 thousand (1.4% of all deaths from cancer).

- In Europe, the estimated standardized incidence of cutaneous melanoma for 2018 is 15.0 per 100,000 people. The estimated standardized mortality from cutaneous melanoma for 2018 in Europe is 1.4 per 100,000 people.
- For Bulgaria, the estimated standardized incidence of cutaneous melanoma for 2018 is 6.2 per 100,000 men and 4.8 per 100,000 women and is lower than the European average (15.8 /100,000 men and 14, 6/100,000 women).

In 2015, 497 new cases of melanoma of the skin were registered, of which 52.5% (261) in men, 47.5% (236) in women. The distribution of newly diagnosed cases by stage of the disease is as follows: in the first stage - 27.8% (138 patients), second stage - 41.9% (208 patients), third stage - 8.2% (41 patients), fourth stage - 8.7% (43 patients), and with unspecified stage - 13.5% (67 patients). The estimated standardized mortality from cutaneous

melanoma for 2018 in Bulgaria is 1.5 per 100, 000 women and 2.6 per 100, 000 men and is lower than the European average. The number of patients died from melanoma of the skin in 2015 was 171 people, of whom 56.1% were men and 43.9% were women. The prevalence data indicate that by 2015 there were 4,379 people with cutaneous melanoma.

Efficacy data

Compared and analyzed data from the following studies were used to evaluate the therapeutic efficacy and safety of Cotellic for the treatment of adult patients with unresectable or metastatic melanoma with the BRAF V600 mutation:

- GO28141
- NO25395

Clinical study GO28141

In the experimental arm, participants received cobimetinib 60 mg orally once daily on days 1-21 of each 28-day cycle and vemurafenib 960 mg orally twice daily on days 1-28 of each 28-day cycle. In the control arm, participants received placebo orally once daily on days 1-21 of each 28-day cycle plus vemurafenib 960 mg orally twice daily on days 1-28 of each 28-day cycle until disease progression, occurrence of unacceptable toxicity, or withdrawal of consent (whichever occurs earliest). Treatment is continued until disease progression, occurrence of unacceptable toxicity, or withdrawal of consent (whichever occurs first).
The median duration of cobimetinib treatment in patients in the experimental arm was 9 months (95% CI 8.1-10.2) for vemurafenib this value was 9.2 months (8.4-11.0). In the control arm, the median duration of treatment with vemurafenib was 5.8 months (95% CI 5.5-7.4).
In both arms of the study, the dose and dosing regimen of cobimetinib and vemurafenib were as described in the SmPC of both products.

Study (identification №, abbreviation, etc.)	GO28141 (NCT01689519/coBRIM/)			
Publications in indexed journals	1. de la Cruz-Merino L, et al. J Transl Med. 2017 Jun 24;15(1):146. 2. Dréno B, et al Ann Oncol. 2017 May 1;28(5):1137-1144. 3. Ascierto PA, et al. The Lancet Oncology. 2016;17(9):1248-60. 4. Larkin J, et al. N Engl J Med. 2014 Nov 13;371(20):1867-76.			
Place of conduction, country	Austria, Belgium, Czech Republic, France, Hungary, Italy, Netherlands, Norway, Spain, United Kingdom, Canada, Russian Federation, Australia, Turkey, New Zealand, Switzerland, Israel, USA, Sweden, Germany			
Design/type of the study	Phase III, randomized, double-blind, placebo-controlled			
Number of the participants	495			
Demographic characteristics of the patients included				
	Intervention (n=247)		Comparison/control (n=248)	
Median age	56 (23-88)		55 (25-85)	
Gender	Men	Women	Men	Women
	146 (59%)	101 (41%)	140 (56%)	108 (44%)
ECOG PS	0	1	0	1
	184/243 (76%)	58/243 (24%)	164/244 (67%)	80/243 (33%)
Metastatic status				
Unresectable stage IIIC	21 (9%)		13 (5%)	
M1a	40 (16%)		40 (16%)	
M1b	40 (16%)		42 (17%)	
M1c	146 (59%)		153 (62%)	
Elevated levels of lactate dehydrogenase	112/242 (46%)		104/242 (43%)	
History of brain metastases	1 (<1%)		2 (<1%)	
BRAF mutation subtipization				

V600E	174 (70%)	170 (69%)
V600K	32(13%)	24 (10%)
Not done	42 (17%)	53 (22%)
Intervention (n=247)	Cobimetinib 60 mg once daily on days 1-21 of each 28-day treatment cycle and vemurafenib 960 mg twice daily on days 1-28 (dose and regimen as described in the SmPC of both products)	
Comparison/control (n=248)	Placebo once daily on days 1-21 of each 28-day treatment cycle and vemurafenib 960 mg twice daily on days 1-28 (dose and regimen as described in the SmPC of the product)	
Primary results	Intervention (n=247)	Comparison/control (n=248)
Median progression-free survival (PFS) as assessed by the investigator (INV), months, (95% CI)	12,3 (9,5–13,4)	7,2 (95%CI 5,6–7,5)
	(HR 0,58 [95% CI 0,46–0,72], p<0,0001) *median follow-up 14.2 months*	
Secondary results	Intervention (n=247)	Comparison/control (n=248)
Median overall survival (OS), months, (95% CI)	22,3 (20,3; NE)	17,4 (15,0; 19,8)
1-year OS, %	74,5	63,8
2-year OS, %	49,1	**38,6**
3-year OS, %	37,4	**31,5**
Objective response rate (ORR), n,%	172 (69,6%)	124 (50,0%)
Best overall answer, n,%		
Complete answer	39 (15,8%)	26 (10,5%)
Partial answer	133 (53,8%)	98 (39,5%)
Objective response, n (%; 95% CI)	172 (70%; 63,5–75,3)	124 (50%; 43,6–56,4)
	p<0,0001	
Stable disease	44 (17,8%)	92 (37,1%)
Median duration of response	13	9,2

(DOR), months, (95% CI)	(11,1–16,6)	(7,5–12,8)
Median PFS, assessed by an independent data review committee (IRF), months	11,3	6,0

Clinical study NO25395

10 cohorts with different dose combinations and regimens of cobimetinib and vemurafenib are planned. In the cohort expansion phase, the number of participants in cohorts IA and IB was increased due to reported good tolerability and safety, reaching the maximum tolerated dose and route of administration for cobimetinib [60 mg once daily 1-21 of each 28-day cycle of treatment (IA), dose and route of administration described in the SmPC of the product] and the approved dose and route of administration of vemurafenib [960 mg twice daily on days 1-28 (IB), dose and route of administration described in the SmPC of the product]. Treatment is continued until disease progression, occurrence of unacceptable toxicity, or withdrawal of consent (whichever occurs first). The median number of cobimetinib and vemurafenib cycles received in untreated patients was 16 (2-50), and in advanced patients this value was 4 (1-50).

Study (identification №, abbreviation, etc.)	NO25395 (NCT01271803/BRIM7)	
Publications in indexed journals	1. Ribas A, et al. Lancet Oncol. 2014 Aug;15(9):954-65. Erratum in: Lancet Oncol. 2014 Sep;15(10):417. 2. Baudy AR, et al. EJNMMI Res. 2012 May 31;2(1):22. 3. Daud, A., et al. 14th International Congress of the Society for Melanoma Research/9th World Congress of Melanoma; October 18–21, 2017; Brisbane, Queensland, Australia.	
Place of conduction, country	Australia and the United States of America	
Design/type of the study	Phase Ib, open-label, dose-escalation study	
Number of the participants	131	
Demographic characteristics of the patients included		
	Patients with progression (n = 66)	Untreated patient (n=63)

Median age	52,5 (19-88)		56,0 (21-74)	
Gender	Men	Women	Men	Women
	42 (63,6%)	24 (36,4%)	35 (55,6%)	28 (44,4%)

ECOG PS 0	23 (35%)	41 (65%)
ECOG PS 1	43 (65%)	22 (35%)
Unresectable stage IIIC	3 (5%)	7 (11%)
Stage IVA	4 (6%)	3 (5%)
Stage IVB	5 (8%)	9(14%)
Stage IVC	54 (82%)	44 (70%)
Elevated levels of lactate dehydrogenase	39 (62%)	29 (46%)
Interventions	10 cohorts with different dose combinations and regimens of cobimetinib and vemurafenib are planned. Cohorts IA and IB have been expanded due to reported good tolerability and safety, reaching the maximum tolerated dose and route of administration for cobimetinib [60 mg once daily 1-21 of each 28-day treatment cycle (IA) *described in the SmPC of the product*] and the approved dose and route of administration of vemurafenib [960 mg twice daily on days 1-28 (IB) *described in the SmPC of the product*].	
Primary results		
DLT (Dose-limiting toxicities)	Dose-limiting toxicities were reported in 3.1% of patients [weakness, QT prolongation, stomatitis, arthralgia and myalgia]. Maximum tolerated dose of the combination of vemurafenib 960 mg twice daily from a 28-day course of treatment and cobimetinib 60 mg once daily on days 1-21 of a 28-day course of treatment.	
Pharmacokinetics	Analysis of pharmacokinetic data showed that vemurafenib exposure was not affected by co-administration of cobimetinib. Similarly, vemurafenib did not alter the pharmacokinetics of cobimetinib. Pharmacokinetic data of the combination of vemurafenib and cobimetinib are comparable to those of cobimetinib alone (maximum drug plasma concentration and area under the concentration-time curve at steady state).	
Safety profile		
Secondary results	Patients with progression (n = 66)	Untreated patients (n=63)
Objective response rate,% (95% CI)	15,2 (7,5-25,5)	87,3 (76,7-94,4)
Complete answer	1,5	**19,0**

Partial answer	13,6	68,3
Stable disease	42,4	9,5
Disease progression	36,4	3,2
Lack of evaluation	6,0	
Metastatic status		
Median DOR	6,7 (4.9- Not evaluable)	12,5 (9,7-Not evaluable)
Median PFS, months	2,8 (2,6-3,4)	13,8 (10,8-20,6)
Median OS, months (95% CI)	8,5 (6,7-11,1)	31,8 (24,5-Not estimable)
1-year OS, % (95% CI)	35,5 (23,7–47,4)	82,5 (73,2–91,9)
2-year OS, % (95% CI)	17,5 (7,6–27,4)	63,9 (51,8–76,1)
3-year OS, % (95% CI)	12,5 (3,3–21,7)	41,5 (28,1–54,8)
4-year OS, % (95% CI)	12,5 (3,3–21,7)	**39,2 (25,8–52,5)**
5-year OS, % (95% CI)	12,5 (3,3–21,7)	**39,2 (25,8–52,5)**

Safety data

Clinical study GO28141

Almost all patients in both groups had at least one adverse event. Serious adverse events were reported in 92 patients (37%) in the cobimetinib and vemurafenib groups, and 69 patients (28%) in the placebo and vemurafenib groups.

Treatment-related adverse events were reported in 241 (98%) of 247 patients in the cobimetinib and vemurafenib arm, and 147 (60%) of patients had treatment-related adverse events (AEs) grade 3 and higher. In the placebo and vemurafenib group, 233 (92%) of 246 patients had treatment-related adverse events, with 128 (52%) of patients with grade 3 or higher AEs.

The incidence of cutaneous squamous cell carcinoma and keratoacanthoma is lower in the arm with the combination compared to the control arm.

Photosensitivity is more common in the arm with the combination - 34%, compared to 20% of patients in the control arm (placebo and vemurafenib). Most of these events are grade 1 and 2, and are affected by topical treatment.

MEK - inhibitor specific AEs in the arm with cobimetinib and vemurafenib include: serous retinopathy, decreased left ventricular ejection function and elevated creatine phosphokinase levels. Serous retinopathy of any grade was observed in 67 (27%) of 247 patients in the

cobimetinib and vemurafenib arm compared with 9 (4%) of 246 patients in the control arm. Most of these events are grade 1-2. Decreased left ventricular ejection fraction grade 2 or higher was found in 28 (11%) of 247 patients in the cobimetinib and vemurafenib arm compared to 12 (5%) of 246 patients in the control arm (placebo and vemurafenib). Elevated levels of creatine phosphokinase grade 3 and higher were reported in 30 (12%) of 247 patients in the cobimetinib and vemurafenib arm compared with one (<1%) in 246 in the control arm.
Treatment discontinuation due to treatment-related AE was reported in 52 (11%) patients in the study: 35 (14%) in the cobimetinib and vemurafenib arm and 17 (7%) in the control arm. The most common reason for discontinuation of treatment in the cobimetinib and vemurafenib arm was elevated aminotransferases and in the control arm elevated γ-glutamyltransferase and weakness.

In the cobimetinib and vemurafenib arm, dose changes due to AEs of vemurafenib were reported in 87 (35%) patients and of cobimetinib in 75 (30%) patients. In the control arm, 72 (29%) patients had a change in vemurafenib dose and 27 (11%) had a placebo dose reduction.

Clinical study NO25395

Adverse events are more common in patients who have never been treated with a BRAF inhibitor than in those after progression on vemurafenib therapy.

The most common adverse events in all patients were: non-acneiform rash (60%), diarrhea (64%), weakness (48%), nausea (45%), photosensitivity (40%) and changes in liver laboratory parameters. (50%). The majority of AEs are mild to moderate in severity. The most common grade 3 and 4 AEs are: cutaneous squamous cell carcinoma (9%), elevated alkaline phosphatase (9%) and anemia (7%). No grade 5 adverse events were reported. Skin squamous cell carcinoma and keratoacanthoma associated with BRAF inhibitor treatment were less common in patients who had progressed after treatment with vemurafenib.

MEK-inhibitor-specific adverse events, such as diarrhea, acneiform rash, elevated creatine phosphokinase, are more common in patients not treated with BRAF inhibitor. Chorioretinopathy, retinopathy, macular edema and retinal detachment as AEs were reported in this group of patients.

The frequency of temporary discontinuation and dose reduction is higher in patients not treated with BRAF inhibitor.

Analysis of data reported by patients

A total of 493 patients from the coBRIM study were included in the safety analysis. The most common ADRs (> 20%) observed more frequently in the shoulder with cobimetinib and vemurafenib were diarrhea, rash, nausea, pyrexia, photosensitivity reactions, increased alanine aminotransferase, increased aspartate amonotransferase, increased creatine

phosphokinase in the blood and vomiting. The most common ADRs (> 20%) observed with increased frequency in the shoulder with placebo and vemurafenib were arthralgia, alopecia and hyperkeratosis. Fatigue was observed with equal frequency in both shoulders.
A total of six deaths in the combination treatment group and three deaths in the control group were due to ADRs. The incidence of toxic events, leading to withdrawal of the treatment was similar (13% in the group with the combination therapy and 12% in the control group).

Comparators data

In the "National medical standards for systemic drug treatment, assessment of therapeutic effect and follow-up of malignant solid tumors in adults" of the Bulgarian Oncological Scientific Society for systemic therapy of recurrent and metastatic disease - as first line of treatment for BRAF V600-mutated tumors is recommended targeted Vemurafenib therapy; Dabrafenib; Dabrafenib + Trametinib or Vemurafenib + Cobimetinib. Combined targeted therapies for the treatment of BRAF V600-mutated tumors are also included in a project of the Pharmacotherapeutic Guide for Medical Oncology. From the targeted therapies for the treatment of BRAF V600-mutated tumors monotherapy regimens with Vemurafenib and Dabrafenib are paid by public funds. The choice of comparators is consistent with the defined target population - patients with unresectable or metastatic melanoma with BRAF-mutation and, accordingly the therapeutic approaches used in this patient population. Therapeutic drug alternatives have been identified - monotherapy with Vemurafenib, monotherapy with Dabrafenib, and a potential comparator includes combination therapy with Dabrafenib + Trametinib.

Pharmacoeconomic indicators

Description of published health technology assessments performed by state institutions for the purposes of another national healthcare system

Evaluation data from the UK, France, Poland, Germany and Scotland are presented, with a positive HAS recommendation in France.

Applied analysis

Applied are: Cost-Effectiveness Analysis (CEA) with Life Years Gained (LYG) outcome and Cost-Utility Analysis (CUA) with Quality-Adjusted Life Year (QALY) outcome. The perspective is on the part of the payer NHIF, with a time horizon of 30 years and discounting - 3.5% per year. Comparative alternatives are vemurafenib and dabrafenib as monotherapy, trametinib + dabrafenib as combination therapy. A survival model was applied to estimate life expectancy, and a Markov model of three health conditions was subsequently developed - a condition free of progression, progression, and death.

The results of the baseline and follow-up analyzes showed that cobimetinib + vemurafenib was not cost-effective compared to dabrafenib or vemurafenib monotherapy, but was cost-effective compared to trametinib + dabrafenib combination therapy. The life-years gained are 0.22, and the acquired QALY is 0.176, the costs of combination therapy with Vemurafenib + Cobimetinib are lower than those with Dabrafenib + Trametinib and the therapy is dominant. Sensitivity analyzes show that the results are sensitive to both changes in costs and changes in efficiency.

Budget impact assessment

National statistics, data from price registers for medicinal products and health services were used to assess the budget impact. The perspective is from the point of view of the National Health Insurance Fund, and the time horizon is 5 years. The costs of drug therapy are included - calculated for the number of cycles and in accordance with the median life expectancy of one patient, predicted in the survival model.
A deterministic sensitivity analysis was performed, which showed that the cost of cobimetinib and its combination was the factor that affected the budget the most. The predicted number of patients is constant in the budgetary impact analysis model and includes 43 to 45 patients per year, with an expected increase in the budget for these patients, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

The addition of cobimetinib to vemurafenib for the treatment of patients with advanced BRAFV600 mutation-positive melanoma is of clear clinical benefit. The combination of cobimetinib and vemurafenib is well tolerated, with an acceptable safety profile and represents a new standard of care.