HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

3 October 2012

The draft opinion approved by the Transparency Committee on 20 June 2012 was examined at a hearing on 3 October 2012

ZELBORAF 240 mg, film-coated tablet
B/56 (CIP code : 220 875-6)

Applicant: ROCHE S.A.S.

vemurafenib (protein kinase inhibitor)
ATC code: L01XE15

List I
Medicine for hospital prescription only.
Prescription restricted to oncologists or doctors competent in oncology.
Medicine requiring special monitoring during treatment.

Date of Marketing Authorisation (European centralised procedure): 17 February 2012

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use

Medical, Economic and Public Health Assessment Division

1 BACKGROUND OF THE EVALUATION

ZELBORAF was given temporary usage authorisation (TUA):

- Temporary usage authorisation by a cohort (cohort TUA): on 20 February 2012, 623 cohort TUAs were issued, including 372 for second-line treatment of metastatic melanoma and a further 222 for first-line treatment of metastatic melanoma and 29 for unresectable melanoma.
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Temporary authorisation for use by a named patient (nominative TUA): on 20 February 2012, 16 nominative TUAs were agreed, including 5 for BRAF V600K mutation-positive metastatic melanoma, 3 for BRAF V600K mutation-positive stage IIIc melanoma and 1 for BRAF V600R mutation-positive metastatic melanoma.

2 CHARACTERISTICS OF THE MEDICINAL PRODUCT

2.1. Active ingredient

Vemurafenib

2.2. Indication

“ZELBORAF is indicated in monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.”

2.3. Dosage

“Treatment with vemurafenib should be initiated and supervised by a qualified physician experienced in the use of anticancer medicinal products.
Before taking vemurafenib, patients must have BRAF V600 mutation-positive tumour status, confirmed by a validated test.

The recommended dose of vemurafenib is 960 mg (4 tablets of 240 mg) twice daily (equivalent to a total daily dose of 1,920 mg). The first dose should be taken in the morning and the second in the evening, approximately 12 hours later. Vemurafenib may be taken with or without food, but consistent intake of both daily doses is recommended.

Duration of treatment:
Treatment with vemurafenib should continue until disease progression or the development of unacceptable toxicity.”

Determination of BRAF mutation status

The diagnostic examination accompanying ZELBORAF/vemurafenib that determines, from a sample rich in cancer cells, whether the BRAF coding gene for a protein kinase situated upstream from the EGFR (Epidermal Growth Factor Receptor) signalling pathway is mutated or not, is currently managed by the French healthcare system and is carried out in 28 cancer molecular genetics hospital platforms (Plateformes hospitalières de génétique moléculaire des cancers) financed by the French National cancer Institute (Institut National du Cancer) and the Directorate General for Care Provisions (DGOS). There is a platform in most regions in France and: "their aim is to perform innovative molecular tests for all patients in the region regardless of the establishment in which they are being treated". The need represented by this examination is thus currently covered by these platforms without any loss of opportunity by the patient. It is not the means by which it is on the list of procedures and benefits pursuant to L. 162-1-7 of the French Social Security Code (i.e. the nomenclature of procedures refundable by national health insurance) that ensures its

financial support. At the current time, inclusion of this examination on the list of procedures and benefits is possible, however, it will require a prior evaluation by HAS.

3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC 2011 Classification

L	Antineoplastic and immunomodulating agents
L01	Antineoplastic agents
L01X	Other antineoplastic agents
L01XE	Tyrosine kinase inhibitors
L01XE15	Vemurafenib

3.2. Medicines in the same therapeutic category

3.2.1. Comparator medicines:

None

3.3. Medicines with a similar therapeutic aim

These are the other therapeutic options used in the treatment of cutaneous melanoma:

1. Chemotherapies:
- BICNU (carmustine),
- DETICENE (dacarbazine) and generics,
- MUPHORAN (fotemustine),
- BELUSTINE (lomustine),

2. Immunotherapies:
ROFERON (interferon alpha-2a)
PROLEUKIN (aldesleukin)

3. Monoclonal antibodies:
YERVOY (Ipilimumab)
“YERVOY is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy”.
Substantial AB / IAB IV in the therapeutic strategy (TC opinion of 14 December 2011)

4 ANALYSIS OF AVAILABLE DATA

The dossier submitted comprises three studies:
- a phase I study (PLX06-02) to investigate the dose, which will not be included in this document.
- a phase II study as a second-line treatment and beyond (NP22657, also called BRIM-2)
- a phase III pivotal study (NO25026 [BRIM-3]) as a first-line treatment.
The results of these two studies are presented below.

4.1. Efficacy

A/ as a first-line treatment

Study NO25026 (BRIM-3)
A randomised, open-label study comparing vemurafenib (ZELBORAF) with dacarbazine in patients with BRAF V600 mutation-positive unresectable stage IIIc or metastatic (stage IV) melanoma as a first-line treatment.

Treatments studied:
- vemurafenib was administered orally, according to a dose regimen of 960 mg twice daily, which is four tablets in the morning and at night, and equivalent to a total daily dose of 1,920 mg.
- dacarbazine was administered intravenously at a dose of 1,000 mg/m² over 60 minutes on Day 1 of every three week cycle.
The two treatments were administered until progression of the disease or toxicity which was judged as unacceptable by the clinical investigator occurred.

Primary study objective

The primary objective of this study was to evaluate the efficacy of vemurafenib compared with that of dacarbazine as a first-line treatment, in terms of overall survival and progression-free survival in patients with BRAF V600 mutation-positive unresectable stage IIIc or metastatic melanoma detected by the COBAS 4800 BRAF mutation V600 mutation test.

Joint primary efficacy endpoints:

- overall survival: defined as the time from randomisation to death from any cause. Patients who were event free on the analysis date were recorded on the date of the latest information. Patients who had no post-inclusion tumour progression were recorded on the date of randomisation;

- progression-free survival: defined as the time between randomisation and disease progression or death from any cause. Patients who were event-free (death or progression) on the analysis date were recorded on the date of the last tumour evaluation. Patients who had no post-inclusion progression were recorded on the date of randomisation;

Method:
Intermediate analysis of overall survival was scheduled after the occurrence of 98 events (deaths). A single analysis was scheduled for the progression-free survival endpoint. This analysis was scheduled to take place at the time of the intermediate analysis of overall survival.

In order to maintain an alpha risk limit of 0.05, the statistical limit required for the difference in terms of overall survival was 0.045, and 0.005 for progression-free survival.

Secondary endpoints:
- best overall response rate, evaluated by investigators: a patient was defined as a responder if they had a confirmed complete or partial response[1] according to RECIST version 1.1 criteria. Evaluable patients who did not fulfil these criteria were considered as non-responders, as were patients who did not receive treatment or those who did not have a post-inclusion evaluation carried out;

- duration of response: evaluated in patients who satisfied the confirmed best overall response rate endpoint and defined as the time between the first complete or partial response and progression of the disease or death from any cause. Patients who were progression-free and alive on the analysis date were recorded on the date of the last tumour evaluation;

- delay in response: evaluated in patients who satisfied the confirmed best overall response rate endpoint and defined as the time between randomisation and the first response;

- safety

The inclusion criteria included:
- aged 18 years or over;
- previously untreated metastatic melanoma confirmed by histology (unresectable stage IIIc confirmed by a surgical oncologist or stage IV according to AJCC criteria);
- treatment naive patients;
- BRAF V600 mutation-positive melanoma detected by the COBAS 4800 BRAF V600 mutation test;
- ECOG performance status of 0 or 1;
- normal haematological, hepatic and renal function;
- life expectancy > 3 months.

Non-inclusion criteria included:
- active lesions to the central nervous system unless they have been permanently treated for more than 3 months without progression and without the need for treatment with a glucocorticoid;
- mean QTc interval ≥ 450 msec on ECG.

Results:

A total of 675 patients were randomised (337 patients in the vemurafenib group and 338 in the dacarbazine group). The median age was 56 years in the vemurafenib group and 52.5 years in the dacarbazine group. The ECOG performance status was similar in the two groups, with 68% of patients having a score of 0 and 32% of patients a score of 1.
The disease was metastatic in 95% of cases. The proportion of patients with an elevated LDH serum level, a poor prognosis factor, was similar in the two treatment groups (42%).

Safety data were from an intermediate analysis (to 30 December 2010) scheduled in the protocol on overall survival. On the date of the analysis, the number of events required (187 events) for a final analysis of progression-free survival had been reached.
On this date, the median survival was 3.75 months [0.3; 10.8] in the vemurafenib group and 2.33 months [<0.1; 10.3] in the dacarbazine group.

[1] Complete response: disappearance of all target lesions, confirmed by a new examination carried out at four weeks (remission); Partial response: decrease by at least 30% of the size of the widest diameter of each target lesion, taking into account as a reference the initial size of the widest diameters, confirmed by a new examination carried out at four weeks.

a/ Joint primary efficacy endpoints: overall survival

Table 1: Efficacy results from the pivotal study of overall survival - a joint primary efficacy endpoint, ITT population, intermediate analysis (*after approximately 3 months of follow-up*)

	vemurafenib (n = 336*)	**dacarbazine (n= 336*)**
Median survival (months)	3.75	2.33
Number of deaths	43	75
Medial overall survival[2] [95% CI]	9.23 [8.05; not achieved]	7.75 [6.28; 10.28]
Hazard Ratio [95% CI] Log-rank p test	0.37 [0.26; 0.55] <0.0001	

***** *The analysis population for overall survival was defined as the randomised ITT population at least 15 days before the cut-off date*

During the main analysis, the median overall survival in the vemurafenib group was estimated at 9.23, 95% CI [8.05; not achieved] months versus 7.75 95% CI [6.28; 10.28] months in the dacarbazine group, which is an absolute increase of 1.48 months in favour of vemurafenib. This result is probably overestimated, given that the study was stopped after an interim analysis.

An analysis of overall survival after an additional 9 months follow-up not scheduled in the protocol (to 03 October 2011) showed a median overall survival estimated at 13.2, 95% CI [12.0; 15.0] months in the vemurafenib group versus 9.6, 95% CI [7.9; 11.8] months in the dacarbazine group, which is an absolute increase of 3.6 months in favour of vemurafenib.

Table 2: Overall survival for previously untreated patients with V600 mutation-positive melanoma based on the date of data collection (N = 338 dacarbazine, N = 337 vemurafenib)

Date of data collection	Treatment	Number of deaths (%)	Hazard Ratio (95% CI)	Number of patients with a "cross over" (%)
30 December 2010	dacarbazine	75 (22)	0.37 (0.26 - 0.55)	0 (not applicable)
	vemurafenib	43 (13)		
31 March 2011	dacarbazine	122 (36)	0.44 (0.33 – 0.59) (g)	50 (15%)
	vemurafenib	78 (23)		
3 October 2011	dacarbazine	175 (52)	0.62 (0.49 – 0.77)(g)	81 (24%)
	vemurafenib	159 (47)		

(g) Results recorded at time of "cross over"
Results not recorded at time of "cross-over": 31 March: HR (95% CI) = 0.47 (0.35 – 0.62); 3 October: HR (95% CI) = 0.67 (0.54 – 0.84)

[2] The result available provides an estimation based on the Kaplan-Meier curve and not through an observation.

b/ Joint primary efficacy endpoint: progression-free survival

On the date of the final analysis of progression-free survival, a total of 286 patients presented with an event (disease progression or death): 104 patients in the vemurafenib group versus 182 patients in the dacarbazine group.
The median progression-free survival was 5.32 [4.86; 6.57] months in the vemurafenib group versus 1.61 [1.58; 1.74] months in the dacarbazine group ($p < 0.0001$), which is an absolute increase of 3.71 months in favour of vemurafenib.

Results for the secondary endpoints:

- percentage best overall response
The percentage best overall response (complete or partial response) was 48.4% (including 47.5% partial responses) in the vemurafenib group versus 5.5% of solely partial responses in the dacarbazine group, $p < 0.0001$.
The percentage of patients with a stable disease was 37% in the vemurafenib group versus 24.1% in the dacarbazine group.

- delay in response
The median delay in response was 1.45 months in the vemurafenib group versus 2.72 months in the dacarbazine group.

- duration of response
The estimation of the median duration of response was 5.49 months in the vemurafenib group and not achieved in the dacarbazine group.

Quality of life was not evaluated prospectively and preliminary data reported in the dossier does not enable any conclusions to be drawn.

B/ As a second-line treatment for melanoma

A non-comparative phase II study NP22657 (BRIM 2) included 132 patients with BRAF V600 mutation-positive metastatic melanoma who had received at least one previous treatment.

The primary efficacy endpoint was the percentage overall response (complete or partial response).

The secondary criteria included:
- duration of the response, defined as the time between the first confirmed response (complete response or partial response) and progression of the disease or death from any cause;
- delay in response, defined as the time between the first treatment and the first confirmed and documented response (complete response or partial response)
- progression-free survival, defined as the time between the first treatment and first documentation of disease progression or death from any cause;
- overall survival, defined as the time between the first treatment and death from any cause;
- safety

Results:

The median age of patients was 52 years and 19% were older than 65 years. The majority of patients were male (61%), Caucasian (99%) and 61% of them had a stage M1c tumour (poor prognosis). Half of patients (51%) had had a failed first-line treatment and 49% had had at least two failed previous treatments (27% had two failed cycles of treatment and 22% had three or more failed cycles of treatment). Of the treatments previously received, 39.4% of patients had interleukin-2 and 5.3% had ipilimumab or tremelimumab, a monoclonal CTLA4 antibody.

During the main analysis carried out after a median follow-up of 6.87 months, the overall response rate (primary endpoint) was 52% (69/132).
The median progression-free survival was 6.1 months. The median overall survival was not achieved on the date of analysis.
An analysis carried out after a median follow-up of 12.9 months showed a similar response rate to that observed in the main analysis (53%) and a median overall survival of 15.9 months.

4.2. Adverse effects

In the pivotal study, treatment was discontinued due to adverse events by 6% of patients in the vemurafenib group versus 4% of patients in the dacarbazine group.
A reduction or suspension in treatment due to adverse events affected 38% (n = 129) of patients in the vemurafenib group versus 9% (n = 25) of patients in the dacarbazine group.
The most common adverse effects in the vemurafenib group (incidence ≥ 30%) were arthralgia (49%), fatigue (33%), skin eruptions (36%), photo-sensitivity reactions (30%), nausea (30%) and alopecia (35%). Each of these events was noted at a frequency of ≤ 4% in the dacarbazine group.
Cutaneous squamous cell carcinoma was reported in 40 patients (12%) in the vemurafenib group and in one patient in the dacarbazine group.
In the phase II study, cutaneous squamous cell carcinoma was reported in 32 patients (24.2%).

4.3. Conclusion

Evaluation of the therapeutic benefit of ZELBORAF (vemurafenib) as a first-line treatment of melanoma is based on an open-label, randomised study that compared vemurafenib with dacarbazine in 675 treatment-naive patients with BRAF V600 mutation-positive, unresectable stage IIIc or metastatic (stage IV) melanoma.
The overall survival and progression-free survival were the joint primary efficacy endpoints.
Efficacy data presented in this dossier are from an intermediate analysis of overall survival scheduled in the protocol. On this date, the number of events required to carry out the final analysis of progression-free survival had been achieved.
The median overall survival in the vemurafenib group was estimated at 9.23 [8.05; not achieved] months versus 7.75 [6.28; 10.28] months in the dacarbazine group, which is an absolute increase of 1.48 months.
Analysis of overall survival after an additional 9 months follow-up (not scheduled in protocol) showed:
- a median overall survival of 13.2 [12.0; 15.0] months in the vemurafenib group versus 9.6 months [7.9; 11.8] in the dacarbazine group, which is an absolute increase of 3.6 months.
The median progression-free survival was 5.32 [4.86; 6.57] months in the vemurafenib group versus 1.61 [1.58; 1.74] months in the dacarbazine group ($p < 0.0001$), which is an absolute increase of 3.71 months in favour of vemurafenib.
The percentage overall response (complete response or partial response) was 48.4% (including 47.5% of partial responses) in the vemurafenib group versus 5.5% of solely partial response in the dacarbazine group, $p < 0.0001$.

The percentage of patients with a stable disease was 37% in the vemurafenib group versus 24.1% in the dacarbazine group.

Within the scope of its use as a second-line treatment and beyond, efficacy and safety data for vemurafenib are based on a non-comparative phase II study. The study included 132 patients with BRAF V600 mutation-positive metastatic melanoma and who had received at least one previous treatment.
During the main analysis carried out after a median follow-up of 6.87 months, the percentage global response (primary endpoint) was 52% (69/132).
The median progression-free survival was 6.1 months and the median overall survival was not achieved on the date of the analysis.
An analysis after a median follow-up of 12.9 months showed a median overall survival of 15.9 months.

Safety data is limited due to the short follow-up period, especially in the pivotal study (median treatment duration of 3 months). Cutaneous squamous carcinomas (approximately 20%) were reported under treatment with vemurafenib. Other events classified as very common (incidence ≥ 30%) were mainly arthralgia, photosensitivity reactions, nausea and alopecia.

5 TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Actual benefit

Melanoma is a skin cancer with a strong metastatic potential which can, when advanced and/or complicated by metastases, be life-threatening in the short or medium term.
It is intended as a curative treatment specifically for melanoma;
The efficacy/adverse effects ratio is modest;
It is a first- or second-line treatment;

Public health benefit:

The public health burden of cutaneous melanoma and other skin cancers is moderate (about 160,000 DALYs). The burden represented by advanced melanomas (unresectable or metastatic) can be regarded as small.
Improvement in the management of patients with skin cancer is a public health need that is an established priority (Cancer Plan 2009-2013).
In view of the available data (in particular a clinical trial versus dacarbazine showing an absolute increase in median overall survival and progression-free survival), the impact of ZELBORAF on morbidity and mortality is considered as moderate. A negative impact on quality of life cannot be ruled out, particularly in view of the safety problems encountered.
In addition, ZELBORAF should therefore be able to provide only a very partial response to the identified public health need.
Consequently, no public health benefit is anticipated for ZELBORAF in this indication.

There are few drug alternatives at this stage of the disease.

Consequently, the actual benefit of ZELBORAF in the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma is substantial.

5.2. Improvement in actual benefit (IAB)

Taking into account:

- an improvement in median overall survival and progression-free survival,
- a safety profile highlighting in particular an increased risk of a second primary skin cancer,
- the targeted nature of the medicinal product,

the Transparency Committee considers that, in the current state of the dossier, ZELBORAF provides a moderate improvement in actual benefit (IAB level III) in the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma.

5.3. Therapeutic use

Metastatic melanomas are associated with an unfavourable prognosis (median survival of 7 months).
Different standard chemotherapies are used in practice: dacarbazine, fotemustine, temozolomide, high doses of IL-2, paclitaxel (off-label) whether or not in combination with cisplatin or carboplatin (off-label), with modest response rates of the order of 20% and complete remission rates of less than 5%.

In patients with stage IV melanoma:

- limited metastases (resectable): surgical resection of the metastases is recommended; on incomplete resection, the use of treatments for the disseminated metastases (described below) can be proposed.

- disseminated metastases (unresectable): the treatment depends on whether or not there are any cerebral metastases.
    - In patients without cerebral metastases: dacarbazine, fotemustine, temozolomide and interleukin in high doses can be used. Combinations of chemotherapy alone (dacarbazine or temozolomide with cisplatin) or combined with a cytokine (IL-2 or interferon alpha) or paclitaxel-based chemotherapies (whether or not in combination with cisplatin or carboplatin) can also be proposed.
    - For patients with cerebral metastases: chemotherapy can be combined with corticosteroids and radiotherapy.

According to the experts, current management is based on selecting patients according to whether or not they have the B-RAF mutation (this mutation is found in 40 to 60% of cases[3,4]); in cases of mutation, the choice of treatment then involves targeted therapy currently provided by vemurafenib.
Recurrences of melanoma are resistant to most of the classic therapeutic agents, particularly dacarbazine or cytokines. Recently, ipilimumab obtained Marketing Authorisation in the treatment of advanced stage melanoma which has failed at least one treatment with chemotherapy. Given developments in the therapeutic strategy, its use appears to be reserved for patients with a tumour that is negative for the B-RAF mutation.

5.4. Target population

The target population of vemurafenib (ZELBORAF) is represented by adult patients with BRAF V600 mutation-positive, unresectable or metastatic melanoma, who have not had previous first- or second-line treatments or more.

Two sub-groups make up the first-line treatment population:

-patients diagnosed immediately with either unresectable stage IIIc or metastatic (IV) melanoma

According to InVS projections for 2011, the number of new cases of melanoma in France is estimated as 9,784 patients.

French data indicates that 1.5% of patients diagnosed with a melanoma are already at the metastatic stage (stage IV).[5] Thus, it can be estimated that the incident population of patients with melanoma diagnosed immediately at the metastatic stage is 147 patients.

-patients diagnosed with a localised stage and who then go on to develop an unresectable or metastatic form represents 20% of cases,[6] which is 1,927 patients.

In total, the number of patients with metastatic melanoma is 2,074.
The ratio between unresectable stage III and stage IV is unknown. It is estimated at 10.6% on the basis if the MELODY study (sample at inclusion of MELODY study, comprising of 195 patients with stage IV and 23 patients with unresectable stage III[7]) and 11.3% based on TUA data for vemurafenib (on 20 February 2012, 29 patients had an unresectable stage IIIc melanoma and 222 had a stage IV melanoma under first-line treatment).
In total, the number of new patients per year with unresectable or metastatic melanoma is estimated at 2,320 patients.
A BRAF V600 mutation is present in 40 to 60% (median rate 50%) of advanced melanomas.
The target population of vemurafenib (ZELBORAF) in the first-line treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma is estimated at 1,200 patients per year.

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[3] Keith T. et al. Inhibition of Mutated, Activated BRAF in Metastatic Melanoma. N Engl J Med 2010; 363: 809-19.
[4] INCa programme for the prospective detection of biomarkers emerging in lung cancer, colorectal cancer and melanoma: a new approach for rapid access to targeted therapies INCA June 2010.
[5] Binder-Foucard F, Olteanu S, Levrat F, et al. Incidence and prevalence of cutaneous melanoma in France: a population based study from eight cancer registries. Abstract ISPOR 2009. Value in Health 2009, Vol. 12, Issue 7, Page A261, PCN28
[6] Committee for Medicinal Products for Human Use (CHMP). Assessment Report For Yervoy (ipilimumab) – EMA 19 May 2011. Procedure No.: EMEA/H/C/002213.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002213/WC500109302.pdf
[7] Transparency Committee opinion for YERVOY (ipilimumab) dated 14 December 2011.

As a second-line treatment, the population for ZELBORAF comprises patients with BRAF V600 mutation-positive metastatic melanoma, and who have not received ZELBORAF as a first-line treatment.
This population can be considered as small, given:

- the change in treatment strategy directed away from diagnosis and towards selecting patients based on the B-RAF mutation
- and the use, for over a year, of vemurafenib within the scope of a TUA as a second-line treatment and beyond.

5.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use by and various public services in the indication and at the dosage in the Marketing Authorisation.

5.5.1. Packaging: Appropriate for the prescription conditions.

5.5.2. Reimbursement rate: 100%