HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

7 May 2014

TAFINLAR 50 mg, hard capsule

Vial (HDPE) of 120 hard capsules (CIP: 34009275496 7 0)

TAFINLAR 75 mg, hard capsule

Vial (HDPE) of 120 hard capsules (CIP: 34009275497 3 1)

Applicant: GLAXOSMITHKLINE

INN	dabrafenib (mesilate)
ATC code (2012)	L01XE (protein kinase inhibitors)
Reason for the request	**Inclusion**
Lists concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital Use** (French Public Health Code L.5123-2)
Indication concerned	**"Dabrafenib is indicated in monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation."**

Actual Benefit	**The actual benefit stated for TAFINLAR is substantial.**
Improvement in Actual Benefit	**TAFINLAR does not provide an improvement in actual benefit (level V, non-existent) in the current treatment of unresectable or metastatic melanoma with a BRAF V600 mutation.**
Therapeutic use	**Dabrafenib (TAFINLAR) is a first-line treatment of unresectable or metastatic melanoma with a BRAF V600 mutation.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation	Date initially granted: 26 August 2013 (European centralised procedure) Temporary authorisation for use by a named patient [ATU nominative in French] prior to the Marketing Authorisation
Prescribing and dispensing conditions/special status	List I Medicine for hospital prescription Medicine requiring special monitoring during treatment. Prescription restricted to cancer treatment or clinical oncology specialists and departments.

ATC Classification	2013	
	L	Antineoplastic and immunomodulating agents
	L01	Antineoplastic agents
	L01X	Other antineoplastic agents
	L01XE	Protein kinase inhibitors
	L01XE23	dabrafenib

02 BACKGROUND

Review of the request for inclusion of TAFINLAR (50 mg and 75 mg, hard capsule) on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use.

Dabrafenib (TAFINLAR) is a RAF protein kinase inhibitor. Oncogenic BRAF mutations lead to a constitutive activation of the RAS/RAF/MEK/ERK pathway. The frequency of BRAF mutations is very high is certain cancers, including 50% for melanomas. The most commonly observed BRAF mutation is the V600E mutation, which represents close to 90% of all BRAF mutations observed in melanomas.

03 THERAPEUTIC INDICATIONS

"Dabrafenib is indicated in monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation."

04 DOSAGE

"Treatment with dabrafenib should be initiated and supervised by a qualified physician experienced in the use of anticancer medicinal products.
Before taking dabrafenib, patients must have confirmation of tumour BRAF V600 mutation using a validated test.

The efficacy and safety of dabrafenib have not been established in patients with melanoma without a BRAF mutation, therefore dabrafenib should not be used in patients with melanoma without a BRAF mutation (see sections 4.4 and 5.1 of the SPC).

Dosage
The recommended dose of dabrafenib is 150 mg (two 75 mg capsules) twice daily (corresponding to a total daily dose of 300 mg). Dabrafenib should be taken at least one hour before, or at least 2 hours after a meal, and leaving an interval of approximately 12 hours between doses. Dabrafenib should be taken at similar times every day to increase patient compliance.

Duration of treatment
Treatment should continue until the patient no longer derives benefit or the development of unacceptable toxicity (see Table 2 of the SPC).
Missed doses
If a dose is missed, it should not be taken if it is less than 6 hours until the next dose.

Dose modifications
Two dabrafenib capsule strengths, 50 mg and 75 mg, are available to effectively manage any dose modification requirements.
The management of adverse reactions may require temporary treatment interruption, dose reduction, or treatment discontinuation (see Tables 1 and 2 of the SPC).
Dose modifications or interruptions are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma (see section 4.4 of the SPC).
Therapy should be interrupted if the patient's temperature is ≥ 38.5°C. Patients should be evaluated for signs and symptoms of infection (see section 4.4 of the SPC).

Recommended dose level reductions and recommendations for dose modifications are provided in Table 1 and Table 2 of the SPC respectively. Dosage adjustments resulting in a dose lower than 50 mg twice daily are not recommended."

05 THERAPEUTIC NEED

Melanoma is a skin cancer with high metastatic potential, associated with the malignant transformation of melanocytes, skin pigment cells.
The survival rate at 5 years ranges from 88% in cases of detection at an early stage, to 18% for unresectable, advanced stage III cases, and less than 5% for stage IV melanomas (metastatic stage).[1]
Current treatment is directed from diagnosis towards selecting patients based on whether or not they have a B-RAF mutation (this mutation is found in 40 to 60% of cases); in cases of mutation, the choice of treatment then involves targeted therapy represented currently by vemurafenib (ZELBORAF) as monotherapy.

06 CLINICALLY RELEVANT COMPARATORS

[1] Survival of patients with cancer in France: Status. http://www.e-cancer.fr/les-soins/4211-survie-des-patients-atteints-de-cancers-en-france-linca-dresse-un-etat-des-lieux.

In the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation, ZELBORAF (vemurafenib) [MA 17 February 2012] is the only medicinal product which is indicated in this context.

NAME (INN) *Company*	Same TC*	Indication	Date of opinion	AB	IAB (Wording)	Reimbursement Yes/No
ZELBORAF (vemurafenib) ROCHE	Yes	in monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma	3/10/2012	substantial	Taking into account: - an improvement in the median overall survival and progression-free survival, - a safety profile that highlights in particular an increased risk of secondary primary skin cancers, -the targeted nature of this medicinal product, the Transparency Committee considers that in the dossier's current state, ZELBORAF provides a moderate improvement in actual benefit (level III) in the treatment strategy for unresectable or metastatic melanoma with a BRAF V600 mutation.	Yes

*therapeutic category

Conclusion

ZELBORAF (vemurafenib) is the clinically relevant comparator for TAFINLAR in the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	Date of MA	Status	Indications
Germany	26.08.13	Start date for reimbursement: 1.10.13	MA indication
United States	29.05.13	Marketed	Indication identical to that in Europe

08 ANALYSIS OF AVAILABLE DATA

The dossier submitted includes two non-comparative studies (BREAK 2 study and BREAK-MB study) and one comparative study (BREAK 3 pivotal study).
A proposal for an indirect comparison versus vemurafenib is included in the "other data" section.

08.1 Efficacy

8.1.1 BREAK-2 Study (BRF113710)

Non-comparative phase II study that evaluated the efficacy of dabrafenib at a dose of 150 mg, taken orally twice daily in patients with melanoma with a BRAF V600E or V600K mutation as a 1st- or 2nd-line treatment at the metastatic stage.

Pre-treated patients could have received treatment for their metastatic disease (including chemotherapy, immunotherapy, targeted therapy, etc.)

The primary study objective was to evaluate the overall response rate for patients with the BRAF V600E mutation.

Secondary endpoints included:
- the overall response rate for patients with the V600K mutation,
- progression-free survival,
- and overall survival.

Tumour responses were evaluated by an independent review board.

Results:

Of the 92 patients included in the study,
- 15 (16%) were treatment naive for their metastatic disease and 77 (84%) had previously received treatment for their metastatic disease (apart from BRAF or MEK inhibitors),
- 76 presented with the V600E BRAF mutation (primary analysis population) and 16 had the V600K mutation. The majority of patients (58/92 patients, i.e. 63%) presented with a stage M1c melanoma,
- 31 (34%) had a LDH level greater than normal values.

In the evaluation made by the independent review board, the overall response rate was 41% for patients with the V600E mutation and 25% in cases of the V600K mutation.
The median progression-free survival was 6.3 months for patients receiving dabrafenib 150 mg twice daily with the V600E mutation. The main efficacy data are summarised in the Table below.

Table 1: Main efficacy data from the BREAK-2 Study

Endpoint	BRAF V600E n = 76	BRAF V600K n = 16
Overall response rate (%) (V600 E primary endpoint)		
Evaluation/INV[a] (95% CI)	59 (48.2 - 70.3)	13 (0 – 28.7)
Evaluation/IRB[a] (95% CI)	41 (29.7 – 51.8)	25 (3.8 - 46.2)
Median progression-free survival (months)		
Evaluation/INV (95% CI)	6.3 (4.6 - 7.7)	4.5 (2.6 – 6.2)
Evaluation/IRB (95% CI)	6.1 (4.6 - NA)	4.5 (2.6 – 6.2)
Median overall survival (months)		
12 months of follow-up[b] (95% CI)	13.1 (10.4 - NA)	12.9 (6.9 - 17.1)

Data from the Clinical Overview for Tafinlar®.
Key: CI: confidence interval; HR: hazard ratio; INV: evaluation by the investigator
IRB: Independent Review Board; NA: Not Achieved
a. Confirmed responses.
b. Analysis updated on 30 April 2012.

8.1.2 BREAK-MB (BRF113929)

A non-comparative, phase II study that evaluated the open label administration of dabrafenib 150 mg twice daily in two cohorts of melanoma patients with cerebral metastases and the BRAF V600E or the V600K mutation.
- Cohort A: patients who had not received treatment for their cerebral metastases.
- Cohort B: patients who previously received a localised treatment (surgery, stereotaxic surgery or radiotherapy) on the brain.

The primary study objective was the evaluation of the Overall Intracranial Response Rate (OIRR) by the investigators for patients with the BRAF V600E mutation.

- The OIRR was defined as the percentage of patients presenting with a complete or partial intracranial response as the best response.
- Patients with no evaluation possible or with missing data for responses were considered as non-responders.
- The OIRR was described for each cohort for the V600E population, with a confidence interval established at 95%.

The secondary objectives were to evaluate the following endpoints:
- the overall response rate (ORR) for V600E and V600K patients: the ORR was defined as the percentage of patients who had a response according to RECIST criteria (complete or partial response). The ORR was calculated by the investigators and by an independent review board based on confirmed responses. To determine the overall response rate, responses outside the central nervous system were added to cerebral responses. Patients with a non-evaluable overall response or with missing response data were considered as non-responders;
- the duration of the responses for V600E and V600K patients;
- the overall intracranial response rate (OIRR) for V600K patients;
- progression-free survival and overall survival for V600E and V600K patients

Results:
Of the 172 patients included, 139 presented with the BRAF V600E mutation, including 74 in cohort A (without prior localised treatment) and 65 in cohort B (previous localised treatment).
The other 33 patients had the V600K mutation, and were split with 15 patients included in cohort A and 18 in cohort B.
The patients included in this study were all stage M1c (metastatic and including at least one cerebral metastasis) in accordance with the study inclusion criteria.
The main results are summarised in the Table below:

Table 2: Main efficacy data from the BREAK-MB Study

Endpoint	**BRAF V600E**		**BRAF V600K**	
	Cohort A **n = 74**	**Cohort B** **n = 65**	**Cohort A** **n = 15**	**Cohort B** **n = 18**
Overall Intracranial response rate (OIRR) % (95% CI)				
Evaluation/INV[a] **(V600E primary endpoint),**	**39 (28 – 51.2)**	**31 (19.9 – 43.4)**	7 (0.2 – 31.9)	22 (6.4 – 47.6)
Median duration of overall intracranial response, weeks (95% CI)				
Evaluation/INV	n = 29 **20.1** (12.0 – NA)	n = 20 **28.1** (20.1 – 28.1)	n = 1 12.4 (NA – NA) [b]	n = 4 16.6 (NA – NA) [b]
Overall Response Rate (ORR) % (95% CI)				
Evaluation/INV[a]	n = 74 37.8 (26.8 – 49.9)	n = 65 30.8 (19.9 – 43.4)	n = 15 0 (0 – 21.8)	n = 18 27.8 (9.7 – 53.5)
Median overall duration of response weeks (95% CI)				
Evaluation/INV	n = 28 22.1 (16.1 – NA)	n = 20 20.1 (20.0 – 28.1)	n = 0 Not applicable	n = 5 3.1 months [c]
Median progression-free survival weeks (95% CI)				
Evaluation/INV	n = 74 16.1 (15.7 – 21.9)	n = 65 16.6 (15.9 – 23.7)	n = 15 8.1 (3.1 – 16.1)	n = 18 15,9 (7.9 – 22.4)
Median overall survival weeks (95% CI)				
	n = 74 33.1 (25.6 – NA)	n = 65 31.4 (25.7 – NA)	n = 15 16.3 (6.9 – 22.4)	n = 18 21.9 (15.3 – NA)

Data from CSR except for [b and c]. [b]: Long GV publication, 2012; [c] : clinical overview

CI: confidence interval; HR: hazard ratio; INV: evaluation by the investigator;
NA : Not Achieved
a. Confirmed responses.

8.1.3 BREAK 3 Study[2]

Phase III, randomised (3:1) study that compared dabrafenib to dacarbazine in patients with advanced melanoma (unresectable stage III or metastatic [stage IV]) not previously treated for these stages and with the BRAF V600E mutation.

The primary efficacy endpoint was overall survival evaluated by the investigators, defined as the time between randomisation and the first date disease progression was observed or death of the patient from any cause.

[2] Hauschild A et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012; 380:358-65.

Among the secondary endpoints:

- progression-free survival evaluated by an independent expert review board,
- overall survival,
- overall response rate (ORR),
- duration of response,
- quality of life (EORTC-QLQ-C30 and EQ-5D),
- safety.

Among the inclusion criteria:

- patients with advanced, unresectable or metastatic melanoma with a V600E mutation,
- patients not pre-treated for their advanced, unresectable or metastatic melanoma (previous treatment with Interleukin 2, surgery or radiotherapy was permitted),
- patients with a performance status between 0-1 and normal haematological, renal, hepatic and cardiac functions.

Among the non-inclusion criteria:

- previous treatment with a BRAF inhibitor or a MEK inhibitor,
- previous anti-cancer treatment for the advanced disease,
- mucosal or ocular melanoma,
- active cerebral metastases,
- history of heart disorders (increased QTc interval, heart failure, coronary syndrome, angioplasty or introduction of a stent, arrhythmia for at least six months, heart valve morphology abnormalities, etc.).

Treatment groups:

- Dabrafenib monotherapy 150 mg twice daily, orally
- Dacarbazine: 1000 mg/m^2 every 3 weeks, intravenously.

Patients are treated until progression, death, unacceptable toxicity or withdrawal of consent by the patient.

Statistical analysis:

Primary objective: comparison of progression-free survival for the groups of patients receiving dabrafenib and dacarbazine respectively on the basis of a reduction by 67% in the risk of progression or death (HR = 0.33; 95% CI) for patients receiving dabrafenib (median PFS of 6 months) compared with patients treated with dacarbazine (median PFS of 2 months) with :

- a power of 99.7% for 102 events observed;
- an overall type I risk of error of 2%;
- randomisation at a ratio of 3 :1, with recruitment of 30 patients per month from the 4th month;
- a loss to follow up rate of 2% in the dabrafenib arm and 10% in the dacarbazine arm

A total of 200 patients needed to be included to observe the 102 events during the 12 months (statistically significant HR expected up to 0.6251). Randomisation stratified by stage: III+IVM1a+IVM1b vs. IVM1c.

Results
A total of 250 patients were included, and their demographic characteristics are described in the Table below.

Table 3: Demographic characteristics of ITT population of patients at inclusion

	Dabrafenib (n = 187)	**Dacarbazine (n = 63)**
Age, median (range, Min-Max)	53.0 (22–93)	50.0 (21–82)
Gender - male	112 (60%)	37 (59%)
Caucasian ethnic origin (%)	187 (100%)	63 (100%)
ECOG performance score at inclusion		
0	124 (66%)	44 (70%)
≥1	62 (33%)	16 (25%)
Unknown	1 (<1%)	3 (5%)
M status on selection		
M0 (stage IIIC inoperable)	6 (3%)	1 (2%)
M1a	23 (12%)	10 (16%)
M1b	34 (18%)	12 (19%)
M1c	124 (66%)	40 (63%)
LDH level (serum Lactate Deshydrogenase) on inclusion :		
Elevated (> the upper limit of normal values)	67 (36%)	19 (30%)
Normal (≤ the upper limit of normal values)	119 (64%)	43 (68%)
Unknown	1 (<1%)	1 (2%)
Previous treatment		
Absence of previous treatment	6 (3%)	1 (2%)
Previous treatment:	181 (97%)	62 (98%)
Immunotherapy	52 (28%)	15 (24%)
Adjuvant radiotherapy,	37 (20%)	10 (16%)
Biological treatment (monoclonal antibodies, vaccines)	3 (2%)	3 (5%)
Adjuvant chemotherapy	1 (<1%)	4 (6%)

Results on the primary efficacy endpoint:

At the time of the primary analysis, the median progression-free survival analysed by the investigators in the dabrafenib group was 5.1 months vs. 2.7 months in the dacarbazine group, which is an absolute increase of 2.4 months (HR = 0.30 (95% CI: [0.18 – 0.51]; p < 0.0001). On this date, the median follow-up period was 5.1 months in the dabrafenib group and 4.8 months in the dacarbazine group.

Similar data were observed for the primary endpoint in the sub-group analysis.
A post-hoc analysis, carried out one year after the primary analysis, suggested a median progression-free survival of 6.9 months in the dabrafenib group versus 2.7 months in the comparator group.

Results of the secondary endpoints:

- Overall survival

On the date of the primary analysis, there was no difference in overall survival between the two groups: overall survival at 6 months of 87% in the dabrafenib group versus 79% in the dacarbazine group, HR = 0.61, (95% CI: [0.25 – 1.48]).

During a post-hoc analysis carried out one year after the primary analysis (point of analysis on 18 December 2012), a comparable number of deaths had been recorded in each of the two

groups: 42% in the dabrafenib group and 44% in the dacarbazine group. On this date, 57% (n = 36) of patients in the dacarbazine group had received dabrafenib (HR to estimate the median overall survival = 0.76; 95% CI: 0.48 – 1.21).

- Overall response rate

The overall response rate evaluated by the investigators was 53% (95% CI: 45.5% - 60.3%) in the dabrafenib group and 19% (95% CI: 10.2% - 30.9%) in the dacarbazine group
Stabilisation (lesions stable for at least 12 weeks) was reported for 40% of patients on dabrafenib and for 30% of patients on dacarbazine.
A post-hoc analysis, carried out one year after the primary analysis, suggested a response rate of 59% in the dabrafenib group versus 24% in the comparator group.

- Quality of life

Quality of life evaluated using the EORTC QLQ-C30 and the EuroQoL EQ-5D questionnaires did not show any difference between the two treatment groups.

8.1.4 Other data

This is an indirect comparison of TAFINLAR (dabrafenib) versus ZELBORAF (vemurafenib) carried out according to the Bucher method from a network including only two studies (Brim 3 for ZELBORAF and BREAK 3 for TAFINLAR); the common comparator was DTIC (dacarbazine).
Interpretation of the results of this indirect comparison should involve the "significant" and the "non-significant" results.
The significant results concern overall survival (potential superiority of ZELBORAF versus TAFINLAR) found in only one of the data sets analysed (according to the cut-off date and by censoring patients at the time of their cross-over), and to a certain extent a better tolerance of TAFINLAR compared with ZELBORAF.
These results should only be considered as being exploratory, given the risk of there being possible potential interaction factors (i.e. homogeneity of Break 3 and Brim 3 study populations vis à vis possible interaction variables). Therefore, the duration of follow-up is different between both the Brim 3 and Break 3 studies, the accompanying test were different for the two studies. In addition, the methodological quality of the Brim 3 study appears to be inferior, in terms of follow-up (open-label) and the declaration of events (fewer than expected).
Finally, given the number of comparisons tested (and not specified beforehand in the protocol), the consummation of the alpha risk was not managed.
With regard to adverse events, they should be considered using what is already known about each of these two substances (TAFINLAR et ZELBORAF) with trials and studies already carried out in other indications.
For the non-significant results, it is the interpretation of this lack of difference that should be discussed here. Such "inconclusive" results are common when it comes to an indirect comparison, as this approach (meta-analytical type) is entirely retrospective and it is therefore impossible, in this context, to guarantee that the power of these indirect comparisons will be sufficient.
This limitation applies to both the evaluation of the efficacy and relative safety. For this second evaluation, this limitation becomes even more problematic; the initial studies have not been designed with a power sufficient enough for the evaluation of the safety endpoints (except in exceptional circumstances where the study objective is specifically to evaluate safety).

In conclusion, and given the points discussed above, it was not possible to highlight from this single indirect comparison of two studies that there was any difference in the risk - benefit ratio between TAFINLAR and ZELBORAF, both in terms of benefits or risk. However, this does not signify that these two treatments are equivalent.

08.2 Safety/Adverse effects

Treatment discontinuations due to adverse events were similar in both groups (3%).
The most commonly reported (>10% of patients) adverse effects for patients who received dabrafenib were hyperkeratosis in 37% (69 patients), headaches in 32% (59 patients), hyperthermia in 28% (52 patients), arthralgia in 27% (51 patients), cutaneous papilloma in 24% (45 patients), palmar–plantar erythrodysaesthesia syndrome in 20% (37 patients), fatigue in 19% (36 patients) and nausea in 19% (36 patients). The most commonly reported adverse events for patients who received dacarbazine were those linked to gastrointestinal and haematological toxicity: nausea (51%), vomiting (25%), anaemia (12%), abdominal pain (14%) and neutropenia (17%).
The incidence of serious adverse events (whether fatal or not) was 26% (150 patients) for patients treated with dabrafenib in the pooled analysis of 578 patients, and 22% (13 patients) for patients treated with dacarbazine in the pivotal study.
Treatment-related serious adverse events were reported for 17% of patients (n=96) treated with dabrafenib and 3% (n = 2) treated with dacarbazine.
The treatment-related serious adverse events most commonly reported with dabrafenib were cutaneous squamous cell carcinoma: 4% (6% in the pooled analysis), pyrexia: 4% (22 patients) and chills: 1% (6 patients). The treatment-related serious adverse events most commonly reported with dacarbazine were nausea: 2% (1 patient), vomiting: 2% (1 patient) and neutropenia: 2% (1 patient).

08.3 Summary & discussion

Evaluation of the therapeutic benefit of TAFINLAR (dabrafenib) as a first-line treatment of melanoma is based on an open-label, randomised study that compared dabrafenib (monotherapy 150 mg twice daily, orally) to dacarbazine (1000 mg/m^2 every 3 weeks, intravenously) in 250 treatment-naive patients with BRAF V600 mutation-positive unresectable stage IIIc or metastatic (stage IV) melanoma.
The primary efficacy endpoint for the study was progression-free survival.

At the time of the primary analysis, the median progression-free survival analysed by the investigators in the dabrafenib group was 5.1 months versus 2.7 months in the dacarbazine group, which is an absolute increase of 2.4 months (HR = 0.30 (95% CI: [0.18 – 0.51]; p < 0.0001). On this date, the median follow-up period was 5.1 months in the dabrafenib group and 4.8 months in the dacarbazine group

On this date, there was no difference in overall survival between the two groups: overall survival at 6 months of 87% in the dabrafenib group versus 79% in the dacarbazine group, HR = 0.61, (95% CI: [0.25 – 1.48]).
During a post-hoc analysis carried out one year after the primary analysis (point of analysis on 18 December 2012), a comparable number of deaths was recorded in each of the two groups: 42% in the dabrafenib group and 44% in the dacarbazine group. On this date, 57% (n = 36) of patients in the dacarbazine group had received dabrafenib (HR to estimate the median overall survival = 0.76; 95% CI: [0.48 – 1.21]).

The overall response rate evaluated by the investigators was 53% (95% CI: [45.5% - 60.3%]) in the dabrafenib group and 19% (95% CI: [10.2% - 30.9%]) in the dacarbazine group. Stabilisation (lesions stable for at least 12 weeks) was reported for 40% of patients on dabrafenib and for 30% of patients on dacarbazine.
Quality of life evaluated using the EORTC QLQ-C30 and the EuroQoL EQ-5D questionnaires did not show any difference between the two treatment groups.

Safety data are limited due to the short follow-up period (approximately 5 months for the pivotal study). The most commonly reported (>10% of patients) adverse events for patients who received dabrafenib were hyperkeratosis, headaches, hyperthermia, arthralgia, cutaneous papilloma and palmar–plantar erythrodysaesthesia syndrome. Cutaneous squamous cell carcinoma were reported for seven patients (4%) in the dabrafenib group, whereas there were no cases in the dacarbazine group.
The most commonly reported (> 10% of patients) adverse events for patients who received dacarbazine were gastrointestinal (nausea 51%, vomiting 25% and abdominal pain 14%) and haematological (anaemia 12% and neutropenia 17%).

An indirect comparison based solely on two studies has been proposed in the dossier. It presents the methodological limitations (see other data section) which does not enable any conclusions to be drawn on the benefit risk ratio between TAFINLAR and ZELBORAF, neither in terms of risks or benefits. However, this does not signify that these two treatments are equivalent.

08.4 Planned studies

8.4.1 Risk management plan (RMP)

The risk management plan provides for the continued monitoring and assessment of all identified and potential risks, via:
- a pharmacovigilance plan: a systematic review of safety data from scheduled studies and those currently in progress for specific events of interest.
- the following studies and analyses:

1/ the BRF113773 study, evaluating the effect of dabrafenib on ECG parameters, including prolongation of QT interval.
2/ the BRF116056 study, evaluating the safety of use and the tolerance of dabrafenib in Japanese patients with the BRAF mutation and a solid tumour.
3/ the BRF115947 phase I pharmacokinetic study in renal and hepatic impairment (National Cancer Institute).
4/ the BRF116313 phase I/II study in the paediatric population.
5/ the BRF116535 phase I bio-comparison study, evaluating the bioavailability of dabrafenib tablets and as a paediatric oral solution following the administration of a single dose in an adult patient presenting with a solid tumour.
6/ 26-week preclinical study on mice.

- risk minimisation activities (specific information in the SPC and the patient information leaflet)

Appendix 1 summarises, for each risk, the various actions implemented within the context of the European RMP.

09 THERAPEUTIC USE[3]

Current treatment for melanomas is directed from diagnosis towards selecting patients based on whether or not they have a B-RAF mutation (this mutation is found in 40 to 60% of cases); in cases of mutation, the choice of treatment then involves targeted therapy, currently represented by vemurafenib (ZELBORAF) as monotherapy.
In this context, dabrafenib (TAFINLAR) is a first-line treatment.

[3] http://www.e-cancer.fr/publications/55-recommandations-de-pratique-clinique/730-rapport-integral-melanome-cutane-metastatique.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual Benefit

- Melanoma is a skin cancer with a strong metastatic potential which can, when advanced, be complicated by metastases or life-threatening in the short or medium term.
- This medicinal product is a curative treatment, specifically for melanoma.
- The efficacy/adverse effects ratio is high.
- There is a treatment alternative represented by Vemurafenib (ZELBORAF)
- This is a first-line therapy.
- Public health benefit:
  In terms of public health, the burden of skin melanomas and other skin cancers is moderate (approximately 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 study versus dacarbazine demonstrating an increase in progression-free survival, with no increase in overall survival, the impact of TAFINLAR on morbidity and mortality is considered as low. A negative impact on quality of life cannot be ruled out, particularly in view of the safety problems encountered.
  Furthermore, TAFINLAR will only provide a very partial response to the identified public health need.
  Consequently, it is not expected that the proprietary medicinal product TAFINLAR will benefit public health in this indication.

Taking account of these points, the Committee considers that the actual benefit of TAFINLAR is substantial in the Marketing Authorisation dosage and indication.

010.2 Improvement in actual benefit (IAB)

TAFINLAR does not provide an improvement in actual benefit (level V, non-existent) in the current treatment of unresectable or metastatic melanoma with a BRAF V600 mutation.

010.3 Target population

The target population of TAFINLAR (dabrafenib) monotherapy corresponds to adult patients with unresectable (IIIc) or as distant metastatic (IV) melanoma with a BRAF V600 mutation. This population therefore corresponds to patients treated receiving first-line treatment for the metastatic stage of their disease.

The population of patients receiving first-line treatment for metastatic disease is comprised of patients diagnosed from the outset at the unresectable, stage IIIc or distant metastatic stage (IV) and patients diagnosed with a localised stage (I, II, IIIa – IIIb) who progress towards an unresectable stage IIIc – IV. According to projections from the French Monitoring Institute (InVS), the number of new melanoma cases was estimated as being 9780 patients in France in 2011 (Francim, 2011)

In France, there is little known about the distribution of cases of melanoma by TNM stage. Data from the eight French registers (Binder-Foucard F, 2009) show that 1.5% of patients with melanoma are diagnosed from the outset at the metastatic stage (IV), which would make the population with the metastatic stage 147 patients (9780 x 1.5%). To this population, patients diagnosed at a localised stage who will progress towards a metastatic stage (IV) need to be added, which represents 20% of cases (Transparency Committee Opinion - ZELBORAF, 2012), i.e. 1927 patients (9780 x 20%). In conclusion, the total number of patients with metastatic melanoma can be estimated as being 2074.

The ratio between the unresectable stage IIIc and stage IV is not known. It can, however, be estimated as being 11.9% based on the Transparency Committee Opinion for ZELBORAF of 2012, i.e. 246 patients (2074 x 11.9%). This would therefore make the population of melanomas at the unresectable stage (IIIc) or the metastatic stage (IV) a maximum of 2320 patients (2074 + 246).

The frequency of the BRAF mutation varies in the literature from 37% for the most recent data (INCa, 2012) and 60% (Menzies et al, 2012a, 2012b) which is a median rate of 49%, and is consistent with the rate of BRAF mutation found for patients tested in the national melanoma cohort, CeNGEPS-GMFMel (52% at the unresectable stage III – IV were tested).

The target population of TAFINLAR in the first-line treatment of unresectable (IIIc) or metastatic (IV) melanoma with a BRAF V600 mutation is estimated as being approximately 1150 patients per year (2320 x 49%).

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion of TAFINLAR (50 mg, 75 mg), hard capsule on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication and at the dosage in the Marketing Authorisation.

◗ Packaging

Appropriate for the prescribing conditions as regards the indication, dosage and treatment duration.

◗ Proposed reimbursement rate: 100%

Appendix 1: , the various actions implemented within the context of the European RMP.

Risks		Actions implemented
Significant **identified** risks	Cutaneous squamous cell carcinoma*	SPC 4.2, 4.4, 4.8 and patient information leaflet/RMP PVP: Systematic review of safety data from scheduled studies and those currently in progress.
	New primary melanoma*	SPC 4.2, 4.4, 4.8 and patient information leaflet/RMP PVP: Targeted follow-up questionnaire to gather information on new melanomas Systematic review of safety data from scheduled studies and those currently in progress.
	Non-cutaneous squamous cell carcinoma/recurrent cancer*	SPC 4.4, 4.8 and patient information leaflet/RMP PVP: Systematic review of safety data from scheduled studies and those currently in progress.
	Pyrexia*	SPC 4.4, 4.8 and patient information leaflet/RMP PVP: Systematic review of safety data from scheduled studies and those currently in progress.
	Renal impairment*	
	Hypersensitivity	SPC 4.3, 4.8 and patient information leaflet/RMP PVP: Systematic review of safety data from scheduled studies and those currently in progress.
	Pancreatitis*	SPC 4.4, 4.8 and patient information leaflet/RMP PVP: Systematic review of safety data from scheduled studies and those currently in progress.
	Uveitis*	SPC 4.4, 4.8 and patient information leaflet/RMP PVP: Systematic review of safety data from scheduled studies and those currently in progress.
	Palmar–plantar erythrodysaesthesia syndrome*	SPC 4.8 and patient information leaflet/RMP PVP: Systematic review of safety data from scheduled studies and those currently in progress.
Significant **potential** risks	Testicular toxicity	SPC 4.6 and patient information leaflet/RMP PVP: Systematic review of safety data from scheduled studies and those currently in progress.
	Increase in the risk of grades 3 and 4 adverse effects, for serious adverse effects and dosage modifications for the elderly (≥ 65 years)	SPC 4.2, 4.8 **and patient information leaflet?/** RMP PVP: Systematic review of safety data from scheduled studies and those currently in progress.
	Off-list use	SPC 4.2, 4.8 and patient information leaflet
	Paediatric population	SPC 4.1, 4.2, 5.3 **and patient information leaflet**/RMP PVP: Paediatric investigation plan approved by EMA (dabrafenib PIP: EMA-001147-PIP01-11).
	Interaction with other medicinal products	SPC 4.4, 4.5 and patient information leaflet/RMP PVP: Systematic review of safety data from scheduled studies and those currently in progress.
Important **missing** information	Use in patients with NYHA stage II, III or IV heart failure	NS
	Safety of use in patients with severe renal impairment	SPC 4.2, 5.2 and patient information leaflet/RMP PVP: Review of the safety data of scheduled studies: BRA115947
	Safety of use in patients with moderate to severe hepatic impairment	
	Non-white population	Review of safety data of the study in progress, BRA116056
	Pregnancy and lactation	SPC 4.6 and patient information leaflet
	Use in patients with reduced cardiac function	**Routine pharmacovigilance**
	Prolongation of QT interval	Review of the safety data of the study in progress, BRA113773
	Risks in patients with an ECOG score of 2 to 4	**Routine pharmacovigilance**
	Detection of rare adverse effects	Systematic review of safety data from scheduled studies and those currently in progress.

Adverse events identified in clinical studies evaluating Dabrafenib in patients with metastatic melanoma. PVP: Pharmacovigilance Plan
Sections of SPC: 4.1 : Therapeutic indications; 4.2: Posology and method of administration ; 4.3 : Contraindications; 4.4: Special warnings and precautions for use; 4.5: Interaction with other medicinal products and other forms of interaction; 4.8: Undesirable Effects; 5.2 Pharmacokinetic properties; 5.3 Preclinical safety data