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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA #	NDA 202806
Applicant Name	GlaxoSmithKline
Date of Submission	July 30, 2012
PDUFA Goal Date	May 30, 2013
Proprietary Name / Established (USAN) Name	Taflinar/ dabrafenib capsules
Dosage Forms / Strength	oral capsules / 50 mg and 75 mg
Proposed Indication(s)	(b) (4) is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation as detected by an FDA approved test. **Limitation of use:** (b) (4) is not recommended for use in patients with wild-type BRAF melanoma."
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Division Director	Patricia Keegan
Regulatory Project Manager Review	Norma Griffin
Medical Officer Review	Marc Theoret
Statistical Review	Weishi (Vivian) Yuan
Non-clinical Pharmacology/Toxicology Review	Alexander Putman
CMC Review	Gaetan Ladouceur (DS), Amit Mitra (DP)
Biopharmaceutics Review	Akm Khairuzzaman
Microbiology Review	Bryan S Riley
Clinical Pharmacology Review	Jian Wang
Pharmacometrics Review	Justin Earp
Pharmacogenomics Review	Christian Grimstein
CDRH/OIVD	Donna Roscoe
OSI	Jean Mulinde
OC	Mahesh Ramandan
CDTL	Suzanne Demko
OPDP	Quynh-Van Tran
OSE/DMEPA	James H. Schlick
OSE/DRISK	Amarilys Vega
Maternal Health Team Consult	Tammie Brent Howard
Office of Medical Policy/Patient Labeling Review	Latonia Ford

CDRH=Center for Devices and Radiologic Health
OIVD= Office of In Vitro Diagnostics
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

On July 30, 2012, GlaxoSmithKline submitted NDA 202806 for dabrafenib for the proposed indication of "unresectable or metastatic melanoma with BRAF V600 mutation as detected by an FDA approved test." Dabrafenib will be the second drug approved for this patient population. Zelboraf (vemurafenib), another RAF kinase inhibitor, was approved for this indication in August 2011.

Dabrafenib mesylate is a RAF kinase inhibitor; based on *in vitro* data, dabrafenib inhibits wild type BRAF, BRAF V600E, BRAF V600K, and BRAF V600D protein kinase activity at clinically relevant concentrations.

The application was supported by a single randomized, open-label, multicenter trial (Protocol PRF113683, BREAK-3) which compared the safety and efficacy of dabrafenib to dacarbazine in patients with previously untreated, unresectable locally advanced or metastatic cutaneous melanoma with BRAF V600E mutations as detected by a clinical trials assay.

BREAK-3 demonstrated a statistically robust and clinically important improvement in progression-free survival (HR 0.33 p<0.001; median PFS of 5.4 months vs. 2.7 months) and a higher response rate (52% vs. 17%) for patients with previously untreated, metastatic or unresectable, BRAF V600E, cutaneous melanoma who were randomized to dabrafenib as compared to those randomized to dacarbazine. In an immature analysis of overall survival (30 deaths), there was no difference in OS and no suggestion of a detrimental effect on OS. The most common serious adverse reactions were an increased risk of new cutaneous squamous cell cancers of the skin (7% vs. none in controls), serious non-infectious, febrile drug reactions (3% grade 3 pyrexia vs. none in controls), and severe hyperglycemia (>250-500 mg/dL) resulting in the need for medical management in non-diabetics or change in medical management of diabetic patients. The most common (incidence ≥ 20%) adverse reactions of dabrafenib were hyperglycemia (50%), hyperkeratosis (37%), hypophosphatemia (35%), headache (32%), arthralgia and papilloma (27% each), alopecia (22%), and palmar plantar erythrodysesthesias (20%).

2. Background

Cutaneous melanoma from malignant transformation of melanocytes in the skin, is the most aggressive malignancy arising from the skin; based on trend analyses, the incidence of melanoma has been increasing over the past several decades. The National Cancer Institute estimates that in 2013 there will be 76, 690 new cases of melanoma and 9,480 deaths due to melanoma in the United States.[1] While 84% of melanoma presents with localized disease which may be cured with surgical excision alone or with adjuvant interferon or investigational agents and has a 5-year survival rate of 98%, for the 4% who present with metastatic disease and receive systemic treatment, the 5-year survival rates is only 15%. Of patients presenting with cutaneous melanoma, approximately 50% will have melanoma bearing BRAF V600 mutations.

There are five drugs that have been approved by the US FDA for the treatment of metastatic melanoma: vemurafenib, ipilimumab, aldesleukin, dacarbazine, and hydroxurea. Hydroxurea which was FDA-approved in the 1970's, is no longer used or recommended by clinical practice guidelines. Dacarbazine and aldesleukin (interleukin-2) were approved by FDA for the treatment of metastatic melanoma in May 1975 and January 1998, respectively, based on evidence of durable objective tumor responses. Their use for the initial treatment of metastatic melanoma has declined following approval of ipilimumab and vemurafenib.

On March 25, 2011, FDA approved ipilimumab (Yervoy, Bristol Myers Squibb) for the treatment of unresectable or metastatic melanoma. Ipilimumab is a fully human IgG1 kappa monoclonal antibody that is directed against the human cytotoxic lymphocyte antigen-4 (CTLA-4) present on activated T-cells. The approval of ipilimumab was based a single, randomized trial which demonstrated a statistically significant improvement in OS for ipilimumab in

[1] http://www.cancer.gov/cancertopics/types/melanoma

combination with a peptide vaccine (gp100 peptides) compared to the peptide vaccine alone [HR 0.66 (95% CI: 0.55, 0.85), p=0.0004] with median survival times of 9.95 months and 6.44 months in the combination and gp100 monotherapy arms, respectively.

On August 17, 2011, vemurafenib (ZELBORAF, Genentech Inc.) an inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAF V600E, was approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test[2]. The approval was based on a single, multicenter, randomized (1:1), open-label, active-controlled (dacarbazine) trial conducted in 675 patients with treatment naive, BRAF V600E mutation-positive unresectable or metastatic melanoma as detected by the cobas 4800 BRAF V600 Mutation Test. The trial demonstrated a statistically significant improvement in OS [HR 0.44 (95% CI: 0.33, 0.59); p < 0.0001] and PFS [HR 0.26 (95% CI: 0.20, 0.33); p <0.0001] for patients in the vemurafenib arm. The median survival time not reached in the vemurafenib arm as compared to 7.9 months in the dacarbazine arm. The median PFS was 5.3 months in the vemurafenib arm compared with 1.6 months in the dacarbazine arm.

Commonly used off-label treatments, whose use has also declined following approval of vemurafenib and ipilimumab, include temozolomide alone or in combination with other drugs, dacarbazine-based combination chemotherapy regimens, and interferon alone or in combination with chemotherapy, as well as investigational immunotherapy treatments.

Relevant Regulatory History:
June 26, 2009: Original IND submission for GSK2118436.

October 7, 2010:

- FDA advised that if another agent receives approval for first-line treatment of BRAF mutation-positive metastatic melanoma based on demonstration of improved survival, an accelerated approval could not be granted.
- GSK noted that following the July 6, 2010 meeting, Protocol BRF113683 was revised such that PFS was the sole primary endpoint. GSK further noted that based on agreements with (b) (4), all patients in the control arm would be allowed to cross-over to dabrafenib at the time of progression. FDA stated that an improvement in PFS of sufficient magnitude may be an appropriate endpoint provided that an improvement in OS is not demonstrated in a prior approval of another drug in GSK's proposed population.
- FDA questioned whether dacarbazine remains an appropriate control and recommended that GSK conduct a 3-arm trial of GSK1120212 alone, dabrafenib alone, and the combination of GSK1120212 and dabrafenib. FDA advised that two pairwise comparisons of monotherapy to combination therapy would allow isolation of the treatment effects (b) (4).

December 30, 2010: Meeting held to discuss the possible submission of an NDA seeking accelerated approval in patients who had received and progressed following prior treatment for BRAF mutation-positive, metastatic melanoma based on evidence of a clinically meaningful response rate, duration of response, and acceptable risk:benefit profile, which would be evaluated in the context of available therapy. FDA stated that a submission containing data on 45 patients, supplemented by additional clinical trial data during the NDA review would be acceptable. FDA also advised that a companion diagnostic test would need to be approved concurrently with the approval of dabrafenib.

[2]http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo

3. CMC/Biopharmaceutics

Chemistry, Manufacturing, and Controls

There are no issues that preclude approval. CMC and biopharmaceutics reviewers have provided an overall acceptability recommendation of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months when stored at 25° C with excursions between 15° C and 30 °C.

4. Nonclinical Pharmacology/Toxicology

There are no pharmacology/toxicology issues that preclude approval.

As noted in the nonclinical review, nonclinical pharmacology studies demonstrated that dabrafenib is an inhibitor of wild-type BRAF (IC50 = 3.2 nM), wild-type CRAF (IC50 = 5nM), and BRAFV600E (IC50 =0.65nM), BRAFV600K (IC50 =0.5nM), and BRAFV600D (IC50 =1.48 nM) kinases. Dabrafenib-induced inhibition of BRAF kinases appeared to be time-dependent, reversible, and ATP-competitive. In vitro incubation with dabrafenib decreased phosphorylation of extracellular signal regulated kinase (ERK) in cell lines. In contrast, in a panel of tumor cell lines, the effects on tumor cell growth (gIC_{50}) was limited to cell lines from some primary cancers containing BRAFV600E mutations but was ineffective in cell growth inhibition for cell lines derived from colon cancer (3 of 4 cell lines), sarcomas, ovarian cancers, and lung cancers bearing BRAF V600E mutations. Dabrafenib was also ineffective in suppression of tumor growth in cell lines with wild-type BRAF or cell lines with KRAS, NRAS, or HRAS mutations.

Repeat dose (13-week) toxicology studies in rats and dogs supported the safety of the proposed recommended human dose (animal exposures 4-fold higher than humans) and the major metabolites of dabrafenib in humans (30-50% of human exposures). The main target organs of toxicity were the skin manifesting as proliferative skin lesions and papules at exposures achievable with the recommended human dose, male reproductive organs consisting of aspermia and degeneration of the testes at exposures achievable with the recommended human dose, heart with development of marked atrophy and hemorrhage in the right atrioventricular at exposures 5-fold greater than that achieved with the recommended human dose, and stomach manifesting as hyperplasia and infiltration. Specifications for impurities and degradants were qualified by 4-week toxicology studies.

Dabrafenib was not mutagenic in the AmesTest or the mouse lymphoma assay, and was not clastogenic in an *in vivo* rat bone marrow micronucleus test. Carcinogenicity studies were not conducted since the indicated population has advanced cancer and clinical trials demonstrated that dabrafenib is carcinogenic (increased incidence of cutaneous squamous cell cancers). Dabrafenib was shown to impair fertility and to be embryotoxic in a combined fertility and embryofetal study in rats.

The non-clinical reviewer recommended approval and did not request PMCs or require PMRs.

5. Clinical Pharmacology

There are no clinical pharmacology issues that preclude approval.

The clinical pharmacology program included single and multiple-dose pharmacokinetic (PK), food effect, mass balance, absolute bioavailability, and drug-drug interactions studies and the results of population PK analysis. Formal QT studies, dedicated DDI studies, and evaluation of PK in patients with severe renal or hepatic impairment were not provided in the NDA. The clinical pharmacology reviewer did not identify any exposure-response (progression-free survival) relationships or exposure-toxicity (evaluated for ≥ grade 3 adverse reactions, and for ≥ grade 3 hyperglycemia, hyponatremia, hypophosphatemia, palmar-plantar erythrodysesthesia and ≥ grade 2 fever). There were no intrinsic factors (age, gender, weight, race) identified that resulted in clinically important effects on the pharmacokinetics of dabrafenib.

Following oral administration of dabrafenib, the median time to achieve peak plasma concentration was 2 hours. Mean absolute bioavailability of oral dabrafenib was 95% in the fasted state however administration of a single 150 mg dose of dabrafenib with a high-fat meal resulted in a 51% reduction in Cmax and 31% reduction in AUC as compared to the fasted state. Dabrafenib is 99.7% bound to human plasma proteins.

The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4; its active metabolites are hydroxy-dabrafenib and desmethyl-dabrafenib, which are also metabolized by CYP3A4, carboxy-dabrafenib which is excreted in bile and urine or decarboxylated. The terminal half-lives of dabrafenib is approximately 8 hours, that of hydroxy-dabrafenib is approximately 10 hours, while those of the carboxy- and desmethyl-metabolites are longer, (21 to 22 hours). Based on exposure, relative potency and PK properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib; the activity of carboxy-dabrafenib is not likely to be clinically meaningful. Fecal excretion is the major route of dabrafenib elimination (71%) and urinary excretion accounts for 23%.

Dabrafenib induces cytochrome P450 isoenzyme (CYP) 3A4-mediated metabolism and may induce other enzymes.

See action letter for post-marketing requirements to address potential safety issues.

6. Clinical Microbiology

There are no microbiology issues that preclude approval.

7. Clinical Efficacy

This NDA is supported primarily by the results of a single trial, Protocol 113683 (BREAK-3), which is a randomized (3:1), two-arm, open-label, active-controlled trial conducted in patients with previously untreated, unresectable or metastatic, BRAF V600E mutation-positive melanoma, as determined by an investigational-use only test at a CLIA-certified centralized testing facility. Randomization was stratified for stage (unresectable stage III, stage IV M1a, and stage IV M1b vs. stage IV M1c).

The primary endpoint of the BREAK-3 trial was investigator-assessed progression-free survival (PFS). Key secondary efficacy objectives were comparison of OS, investigator-assessed ORR and DOR between the two treatment arm, and validation of a BRAF V600E mutation assay as a companion diagnostic test. Additional endpoints were determination of the response rate and duration in patients randomized to dacarbazine who received dabrafenib as second-line therapy, comparison of changes in patient-reported outcomes between the treatment arms, characterization of the toxicity, notably rate of non-melanoma skin lesions in both arms, and of the PK profile of dabrafenib and several exploratory analyses.

Patients were randomized to receive dacarbazine 1000mg/m^2 intravenously on day 1 of each 21-day cycle (control) or dabrafenib 150 mg orally, one hour before or two hours after eating, twice daily (experimental).

Results

A total of 250 patients were enrolled across 70 investigative sites, with 187 patients assigned to dabrafenib and 63 patients assigned to dacarbazine. Baseline demographics were similar in the two treatment arms. Nearly all patients (99%) were White, 60% were male, and 79% were less than 65 years of age. With regard to baseline disease characteristics, 67% had an ECOG PS of 0, 31% had an ECOG PS of 1, and 2% had an ECOG PS of 2; 66% had Stage IV M1c disease, 33% had an LDH value above the upper limit of normal, 60% had both visceral and non-visceral sites of disease while 12% had visceral disease only, and 48% of patients had 3 or more sites of disease.

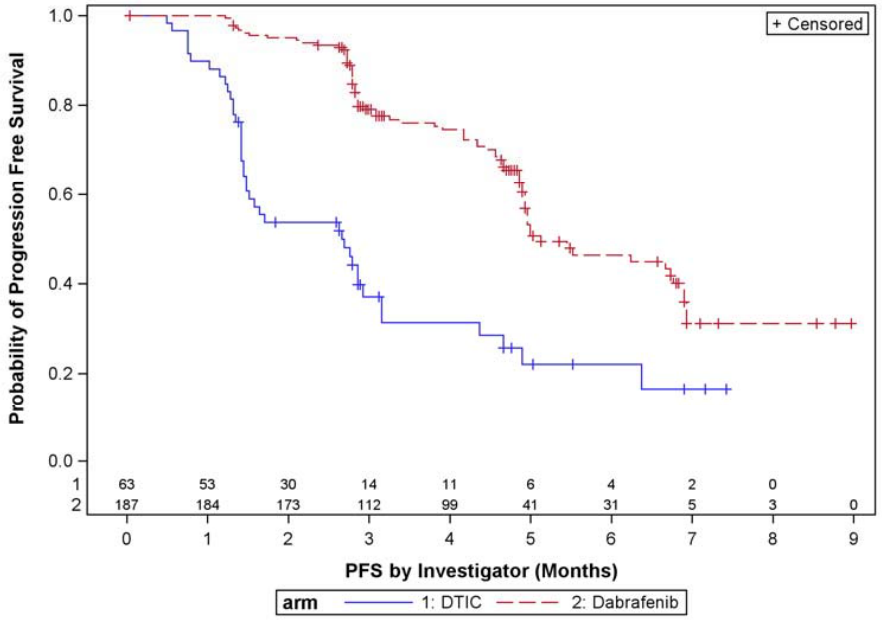
The trial demonstrated a statistically significant and clinically meaningful improvement in PFS for the dabrafenib arm compared to the dacarbazine arm as well as a higher ORR for dabrafenib compared to dacarbazine. The key efficacy endpoints are summarized in the following table and figures.

TABLE 1: Key Efficacy Outcomes in the BREAK-3 Trial

Efficacy Outcome	Dabrafenib (n=187)	Dacarbazine (n=63)
Progression-free survival[1]		
Number of PFS events	78 (42%)	41 (65%)
Number of disease progression events	76	41
Number of deaths	2	0
Hazard ratio[2] (95% confidence interval) p-value[3]	0.32 (0.19, 0.53) P<0.001	
Median PFS in months	5.1	2.7
Overall survival		
Number of deaths (%)	21 (11%)	9 (14%)
Hazard ratio[2] (95% confidence interval) p-value	0.67 (0.28, 1.58) 0.31	
Overall Response Rate[1] (95% confidence interval)	52% (44%, 59%)	17% (9%, 29%)
Complete responses (rate)	6 (3%)	0
Partial Responses (rate)	91 (49%)	11 (17%)

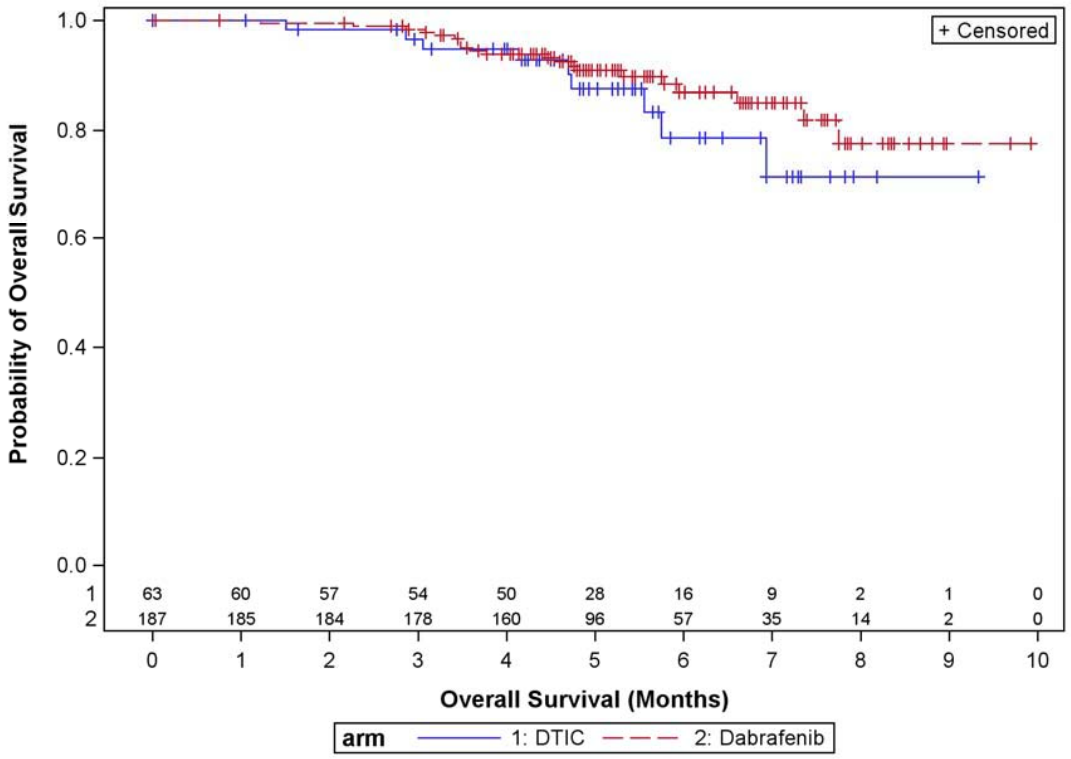
[1] Investigator-assessed
[2] Pike estimator, unstratified
[3] Unstratified log-rank test

Figure 3. K-M Curves of PFS by investigator (from statistical review)



The analysis of OS, provided at FDA's request, was not mature. At the time of the analysis, there were 30 deaths, constituting 12% of the study population. There was no evidence of a detrimental effect of dabrafenib treatment of survival in this assessment.

Figure 6. K-M Curves of OS



The ORR was also higher in the dabrafenib arm as compared to dacarbazine by all assessors (investigator, IRC IR and IRC IR IO), however for those did respond, response durations were similar for patients in both treatment arms. Given the absence of a prespecified plan for multiplicity adjustment and the absence of a statistically significant effect on survival at this time, formal statistical comparisons are not appropriate for secondary outcomes including ORR.

8. Safety

The safety of TAFINLAR was evaluated in 586 patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma, previously treated or untreated, who received TAFINLAR 150 mg orally twice daily as monotherapy until disease progression or unacceptable toxicity, including 181 patients treated for at least 6 months and 86 additional patients treated for more than 12 months.

The most clinically important risks of dabrafenib are an increased risk of developing new cutaneous squamous cell carcinomas (cuSCC) ((5%) developing new cuSCC in the dabrafenib arm of the BREAK-3 trial as compared to none in the dacarbazine arm), new keratoacanthomas ((3%) in the dabrafenib arm compared to none in the dacarbazine arm), basal cell carcinomas ((3%) in the dabrafenib arm compared to none in the dacarbazine arm), and new primary melanomas ((2%) in the dabrafenib arm compared with one in the dacarbazine arm). The one case of melanoma in the dacarbazine arm was identified 16 days after initiation of treatment and thus unlikely to have been drug-related. Across the 586 patient safety database, the incidence of new cuSCC was 11% (64/586) and the incidence of new primary melanomas was 1% (6/586).

An additional clinically significant risk in the indicated patient population, which is suggested by non-clinical studies but has not been confirmed in human subjects, is the risk of cardiac valvular disease. However, as detected through serial LVEF monitoring in BREAK-3, there was an increased incidence in left ventricular dysfunction with clinically significant decreases in LVEF (≥10% below the institutional lower limit of normal) in four dabrafenib-treated patients compared to none in the dacarbazine arm; of the four dabrafenib-treated patients, only one had a history of cardiac disease.

In BREAK-3, the most common serious adverse reactions of dabrafenib are drug-induced febrile reactions, particularly when complicated by dehydration and pre-renal azotemia, and embryofetal teratogenicity.

Also in BREAK-3, 3% of dabrafenib-treated patients discontinued treatment due to adverse reactions and 18% required dabrafenib dose reductions for adverse reactions. The most frequent adverse reactions leading to dose reduction of dabrafenib were pyrexia (9%), PPES (3%), chills (3%), fatigue (2%), and headache (2%). It is noted that patients did not discontinue dabrafenib upon the development of a second primary cancer.

REMS

Clinical reviewers and DRISK concluded that a REMS is not required to ensure safe use of dabrafenib. GSK submitted a risk management plan consisting of professional and patient labeling and did not submit a REMS. This is similar to the approach taken by the manufacturer of the other product in this class, vemurafenib. Both products carry the serious risk of an increased incidence of second primary cancers, specifically primary squamous cell cancers of the skin and keratoacanthomas, as well as a possible increased risk of new primary melanomas. These risks cannot be mitigated by patient selection as there have been no factors identified which predict these increased risks. Additional training is not required as the health professionals prescribing this product (oncologists) are trained to identify these lesions, and professional labeling accurately describes these risks and steps for patient monitoring.

PMRs and PMCs

There are several PMRs to further characterize the risks of dabrafenib. Please see action letter.

9. Advisory Committee Meeting

This NDA was not referred for review to ODAC because this is not the first drug (BRAF inhibitor) in its class, there were no issues related to the clinical trial design or primary endpoint used, and there were no novel issues that would benefit from discussion at ODAC.

10. Pediatrics

Orphan drug designation was granted for dabrafenib for treatment of BRAF V600 mutation positive Stage IIb through IV melanoma. Therefore, this application is exempt from PREA requirements.

11. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval.

- Risk Benefit Assessment: Dabrafenib will be indicated to treat a serious and life-threatening disease for which there are effective but not curative therapies. The clinical benefits of dabrafenib include a clinically meaningful improvement in PFS [HR 0.32 (95% CI: 0.19, 0.53), p<0.001] with an increase in median PFS from 2.7 months with dacarbazine to 5.1 months with dabrafenib, and an substantial increase in ORR (52% vs. 17%) compared to dacarbazine. These results are similar to that seen with the other drug in this class, vemurafenib. The side effect profile of dabrafenib includes increased risks of second cutaneous malignancies and of uveitis, embryofetal toxicity, and possible tumor promotion for BRAF wild type melanoma which have also been seen with vemurafenib. These adverse reactions are considered acceptable in light of the seriousness of the disease

(metastatic melanoma) and observed benefits in terms of reduction in tumor/delay in tumor growth. Both drugs in this class have additional serious adverse reactions which include the risks of febrile drug reactions, pancreatitis, and hyperglycemia with dabrafenib and the risks of QT prolongation, serious dermatologic reactions (TEN, Stevens Johnson syndrome) and photosensitivity with vemurafenib. Therefore, although the effects of dabrafenib on survival have not been established, it may be a reasonable alternative particularly patients who develop QT prolongation or severe skin reactions. Considering all of the above information, dabrafenib treatment provides a favorable risk:benefit assessment for the treatment of patients with BRAF V600E metastatic melanoma. The risk:benefit profile was also discussed in the reviews of Dr. Keegan, Ms. Demko and Dr. Theoret and I concur with their assessment.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:
  I concur with the division and DRISK that a REMS is not required to ensure safe use and the physician and patient labeling will convey information necessary to mitigate the serious risk of secondary cutaneous malignancies.

- Recommendation for other Postmarketing Requirements and Commitments: See action letter.

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/s/

TAMY E KIM
05/28/2013

RICHARD PAZDUR
05/28/2013