CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202429Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	August 16, 2011
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 202429
Applicant Name	Hoffman-La Roche
Date of Submission	4/28/11
PDUFA Goal Date	10/28/11
Proprietary Name / **Established (USAN) Name**	ZELBORAF vemurafenib
Dosage Forms / Strength	Film-coated tablet, 240 mg
Proposed Indication(s)	ZELBORAF™ is indicated for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation as detected by an FDA-approved test. Limitation of Use: ZELBORAF is not recommended for use in patients with wild-type BRAF melanoma.
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Geoffrey Kim (efficacy), Amy McKee (safety)
Statistical Review	Qiang Xu, Shenghui Tang, Rajeshwari Sridhara
Pharmacology Toxicology Review	W. David McGuinn, Robeena M. Aziz, Whitney Helms
CMC Review/OBP Review	Anne Marie Russell, Richard Lostritto
Microbiology Review	N/A
Clinical Pharmacology Review	Jeanne Fourie Zirkelbach
DDMAC	Marybeth Toscano
DSI	Robert Young
CDTL Review	Yangmin Max Ning, John R. Johnson
OSE/DMEPA	Lubna Merchant
OSE/DDRE	N/A
OSE/DRISK	Latonia Ford, Joyce Weaver
Other: QT-IRT	Joo Leon Lee

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

This new drug application for Zelboraf (vemurafenib) tablets was submitted on 4/28/11 for the proposed indication of "treatment of unresectable or metastatic BRAF mutation-positive melanoma by the cobas® 4800 V600 Mutation Test." Because of the improvement in overall survival, the application was given a priority review designation resulting in a PDUFA date of 10/28/11. In addition, because of the paucity of effective therapies for patients with this disease, this application was given an expedited review. The only other treatment which has demonstrated a survival improvement in this disease is ipilimumab which was approved earlier this year. This review will summarize the regulatory history, the clinical trial results which were submitted in support of application, and the recommendations of each review discipline.

2. Background

Zelboraf's mechanism of action is described in the following excerpt from the agreed upon package insert.

> Vemurafenib is a low molecular weight, orally available, inhibitor of some mutated forms of BRAF serine-threonine kinase, including $BRAF^{V600E}$. Vemurafenib also inhibits other kinases in vitro such as CRAF, ARAF, wild-type BRAF, SRMS, ACK1, MAP4K5 and FGR at similar concentrations. Some mutations in the BRAF gene including V600E result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation. Vemurafenib has anti-tumor effects in cellular and animal models of melanomas with mutated $BRAF^{V600E}$.

The IND for vemurafenib (also known as PLX4032, RG7204 and RO51585426) was submitted in 9/06. The phase 1 trial with an extension phase in patients with metastatic melanoma with the BRAF V600E mutation was conducted between 11/06 and 6/10. The phase 2 dosing regimen was determined to be 960 mg BID.

At an end-of-phase 1 meeting in 5/09, the sponsor proposed to develop the drug in patients with advanced melanoma with the $BRAF^{V600E}$ mutation and to use a response rate of ≥30% or PFS (HR 0.5 and an improvement in medial PFS of 2 months) as regulatory endpoints for accelerated approval. The proposal was based on tumor responses in 11 of 16 patients (69%) with advanced melanoma positive for the $BRAF^{V600E}$ mutation in the phase 1 trial. At that meeting the FDA recommended that the sponsor conduct a randomized phase 3 trial with overall survival as the primary endpoint but expressed willingness to discuss use of their

single-arm phase 1 and 2 trials to support accelerated approval once they had more data suggesting impressive activity. At that meeting issues regarding the development of a companion diagnostic to detect the $BRAF^{V600E}$ mutation were discussed.

A phase 2 trial in 132 patients with metastatic melanoma with the BRAF V600E mutation was conducted from 9/09 to 9/10. The applicant shared the preliminary results of this trial with the Agency in August 2010. The objective response rate was reported to be approximately 50%. Also the results of the extension phase of the phase 1 trial were reported in the 8/26/10 issue of the New England Journal of Medicine. Twenty-six of 32 patients (81%) had an objective response.

The BRIM3 trial was a randomized phase 3 trial of vemurafenib vs. darcabazine in patients with previously untreated unresectable or metastatic melanoma with the BRAF V600E mutation. The following excerpt from the Statistical Division Director's Memo summarizes the design and evolution of the trial.

> The phase 3 randomized, controlled, multicenter clinical trial was originally designed (September 2009) with 680 patients (468 events) to detect a difference in median overall survival of 10.7 months in the vemurafenib arm vs. 8 months in the DTIC arm and HR of 0.75 with 80% power and two-sided 2.5% level of significance, accounting for 2 interim analyses with 50% and 75% of information. Overall survival was the primary efficacy endpoint.
>
> In August of 2010 the Agency became aware of the preliminary results of the Phase 2 study as well as the published results of the Phase 1 study. At this time both studies showed impressive objective response rates of > 50% in the targeted population of patients with metastatic melanoma whose tumors harbored BRAF V600E mutation. It was also reported that in the extension phase of the Phase 1 trial, the median progression-free survival among the 32 patients was greater than 7 months. Literature review suggested that the objective response rates ranged from 11% to 24% in metastatic melanoma patients treated with a variety of chemotherapy agents. Given these results the Agency proactively communicated with the applicant multiple times to modify the statistical analysis plan of the phase 3 trial (which had accrued approximately 400 patients at that time and about 300 more patients had been screened to enter the study), adapting with the impressive observed activity of vemurafenib in the phase 1 and phase 2 studies. Specifically the Agency advised the applicant to (1) increase overall study alpha level to two-sided 5% from two-sided 2.5%, (2) set up alpha spending rule with higher probability to cross at interim analysis, (3) less conservative target HR (0.65 instead of 0.75) to be detected, and (4) add progression-free survival as a second primary endpoint. The applicant accordingly revised the statistical analysis plan to conduct final progression-free survival analysis with 187 events at which time an interim survival analysis was to be conducted with 98 deaths (50% information per modified estimates). Although patients were enrolled into the study within a very short period of time at an unexpected high rate of accrual and hence could not reduce the actual number of patients enrolled with the adaptation, the

applicant was able to successfully conduct the analysis early in a planned manner with the timely adaptation of the clinical trial…

The following is a chronology of interactions between the FDA and sponsor regarding the phase 3 trial and is based on a summary provided by Roche.

- Teleconference regarding Phase 3 trial (August 11, 2010):
  - Agency's position on the Phase 3 trial:
    - The original design of the Phase 3 trial was appropriate based on the preliminary Phase 1 data.
    - Emerging data from the Phase 1 melanoma extension cohort with an ORR of 81% suggests unprecedented activity of vemurafenib in metastatic melanoma.
  - Agency questioned whether the Phase 3 trial should continue as originally designed based on new evidence of vemurafenib activity.
    - Requested earlier interim analysis (IA) of OS.
  - Agency requested that Roche keep them informed of when they plan to open an Early Access Program (EAP).
- Teleconference regarding Phase 3 trial (August 18, 2010):
  - Agency requested the interim Phase 3 response rate and duration results, and the number of deaths in each treatment arm to be included in the NDA (based on Phase 2 study).
  - Results of the planned interim OS analysis (based on 50% of accrued events) should be submitted during the NDA review period.
  - Based on plans to publicly release results of Phase 2 trial in early November at SMR conference, FDA recommended that Roche prepare an EAP.
- Teleconference regarding Phase 3 trial (September 14, 2010):
  - Agency requested a meeting with Roche on September 23, 2010 to discuss continuing the Phase 3 trial as currently designed.
  - Agency wants to work with Roche to ensure that they have an organized plan that will capture efficacy data in all patients treated to date.
    - The Agency suggested that the current treatment effect size in the Phase 3 trial is too conservative.
    - The Agency requested that Roche present different scenarios for estimating treatment effect on overall survival based on new information from the Phase 1 and Phase 2 trials. These analyses would not incur a statistical penalty.
    - An improvement in overall survival, together with consistency of best overall response rates and progression-free survival (PFS) in Phase 1, Phase 2 and Phase 3 trials, could serve as the basis for full approval.
    - The Division requested that Roche work on implementing an EAP as soon as possible.
- Teleconference regarding Phase 3 trial (September 20, 2010):
  - The Agency recommended that Roche include an analysis of Phase 3 data including progression-free survival, response rate, and overall survival in the

NDA. Based on the data seen to date, the PFS effect should be large enough to support full approval and that an OS benefit would not be needed.
    - The Agency recommended that Roche consider several scenarios for giving patients access to vemurafenib (options are not mutually exclusive):
        - Close enrollment of the Phase 3 (BRIM3) trial in US sites and allow patients in the control arm to crossover to the vemurafenib arm
        - Reopen enrollment of the Phase 2 (BRIM2) trial
        - Change the primary endpoint of the Phase 3 trial to PFS and allow patients in the control arm to crossover to vemuafenib
- Meeting regarding Phase 3 trial (September 23, 2010):
    - Dr. Pazdur and the review team expressed their desire to work with Roche on a proposal that would allow gathering the data necessary to ensure patient access.
    - FDA agreed to Roche's proposal for an early interim analysis, but requested that the statistical assumptions be relaxed to increase the probability of a positive first interim analysis.
    - FDA strongly advocated opening an expanded access protocol with a broader patient population and/or reopening BRIM-2 to ensure patient access as soon as possible.
    - Post-meeting notes: FDA requested a teleconference to discuss a new SAP with relaxed statistical assumptions on September 28, 2010, and a follow-up teleconference on September 29, 2010.
- Teleconference regarding new Phase 3 Statistical Analysis Plan (September 28, 2010):
    - Agreement on statistical assumptions for OS analyses.
    - Requested that patients in the control arm be allowed to crossover upon progression to active treatment at the time of the projected clinical cutoff for the interim analysis.
- Teleconference regarding Phase 3 Statistical Analysis Plan and EAP (September 29, 2010):
    - Discussion focused on the regulatory path for full approval if the first interim analysis for OS does not cross the statistical boundary, and whether crossover of patients in the control arm to vemurafenib would be a data driven decision based on the results of the IA.
    - The Agency suggested changing the primary endpoint to PFS, which could support full approval assuming a clinically meaningful PFS benefit. Patients in the control arm would be allowed to crossover upon progression.
    - The Agency agreed to review a counterproposal by Roche with hierarchical analysis of the co-primary endpoints of PFS and OS. A significant effect demonstrated in PFS would trigger an IA analysis of OS. If OS does not cross the boundary in the IA, a second and final OS analysis would be conducted earlier than originally proposed. Crossover of patients in the control arm would be contingent upon a positive outcome of the OS analysis.
    - The Agency also requested submission of the draft EAP protocol.
- Submission of BRIM3 revised SAP (October 1, 2010)
- FDA comments on BRIM3 revised SAP received (October 13, 2010)
- Teleconference regarding plans for the BRIM3 Interim Analysis and opening of the US Early Access Protocol (EAP) (November 3, 2010):

- FDA was in agreement with the Phase 3 Statistical Analysis Plan (SAP), protocol amendment and DSMB Charter, the latter having been revised to reflect guidelines for recommending crossover of patients from the dacarbazine arm to the vemurafenib arm based on statistical criteria for PFS and OS. The Division asked that the SAP and protocol amendment cross-reference the DSMB Charter for the crossover criteria.
- FDA indicated that they did not expect any further comments on the EAP and agreed to confirm this in the next couple of days. Roche communicated that they were working to finalize the EAP, including incorporation of comments, and would submit the final protocol shortly after receiving confirmation of the end of the review. Roche also communicated that they were working diligently to open an EAP site as soon as possible.

A treatment protocol was submitted on 10/11/10 and was allowed to proceed on 11/5/10.

At the pre-NDA meeting on 1/21/11, the sponsor proposed to submit an application for accelerated approval based objective response rates from the phase 1 and 2 trials or an application for full approval based on final PFS and interim OS results from the randomized trial. The Agency agreed to review the application under either scenario.

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance and with the following comment on expiry for the approval letter.

> Based on the stability data provided in your application, the drug product is granted a twelve (12) month expiry when stored at USP controlled room temperature 20-25ºC (68-77ºF); excursions permitted to 15-30ºC (59-86ºF). As agreed, validation batches M0020, M0021 and M0022 only are granted a twenty-four (24) month expiry at USP controlled room temperature provided you submit quarterly (every three months) stability updates for these three batches, as general correspondences to the NDA, through the 24-month expiry.

Manufacturing site inspections were acceptable. There are no outstanding issues.

The cobas® 4800 V600 Mutation Test is a companion diagnostic that has been reviewed by CDRH and will be approved at the same time as Zelboraf.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology and biopharmaceutics reviewers that there are no outstanding issues that preclude approval. I also concur with the PMR's recommended by Clinical Pharmacology (see section 13). See the Clinical Review and CDTL Review for summaries of the clinical pharmacology of vemurafenib.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The following summary of the designs and results of the phase 2 and 3 trials that support approval is from the agreed upon package insert.

> The efficacy and safety of ZELBORAF in patients with treatment naive, $BRAF^{V600E}$ mutation-positive unresectable or metastatic melanoma as detected by the cobas® 4800 BRAF V600 Mutation Test were assessed in an international, randomized, open-label trial (Trial 1). The trial enrolled 675 patients; 337 were allocated to receive ZELBORAF 960 mg by mouth twice daily and 338 to receive dacarbazine 1000 mg/m^2 intravenously on Day 1 every 3 weeks. Randomization was stratified according to disease stage, lactate dehydrogenase (LDH), ECOG performance status and geographic region. Treatment continued until disease progression, unacceptable toxicity, and/or consent withdrawal. The major efficacy outcome measures of the trial were overall survival (OS) and investigator-assessed progression-free survival (PFS). Other outcome measures included confirmed investigator-assessed best overall response rate.
>
> Baseline characteristics were balanced between treatment groups. Most patients were male (56%) and Caucasian (99%), the median age was 54 years (24% were ≥ 65 years), all patients had ECOG performance status of 0 or 1, and the majority of patients had metastatic disease (95%).
>
> Efficacy results are summarized in Table 1 and Figure 1.

Table 1 Efficacy of ZELBORAF in Treatment Naive Patients with BRAF^{V600E} Mutation-Positive Melanoma[a]

	ZELBORAF (N=337)	Dacarbazine (N=338)	p-value[d]
Overall Survival			
Number of Deaths	78 (23%)	121 (36%)	
Hazard Ratio (95% CI)[b]	0.44 (0.33, 0.59)		<0.0001
Median Survival (months) (95 % CI)[c]	Not Reached (9.6, Not Reached)	7.9 (7.3, 9.6)	-
Median Follow-up (months) (range)	6.2 (0.4, 13.9)	4.5 (<0.1, 11.7)	
Progression-free survival Hazard Ratio (95% CI)[b]	0.26 (0.20, 0.33)		<0.0001
Median PFS (months) (95% CI)[c]	5.3 (4.9, 6.6)	1.6 (1.6, 1.7)	-

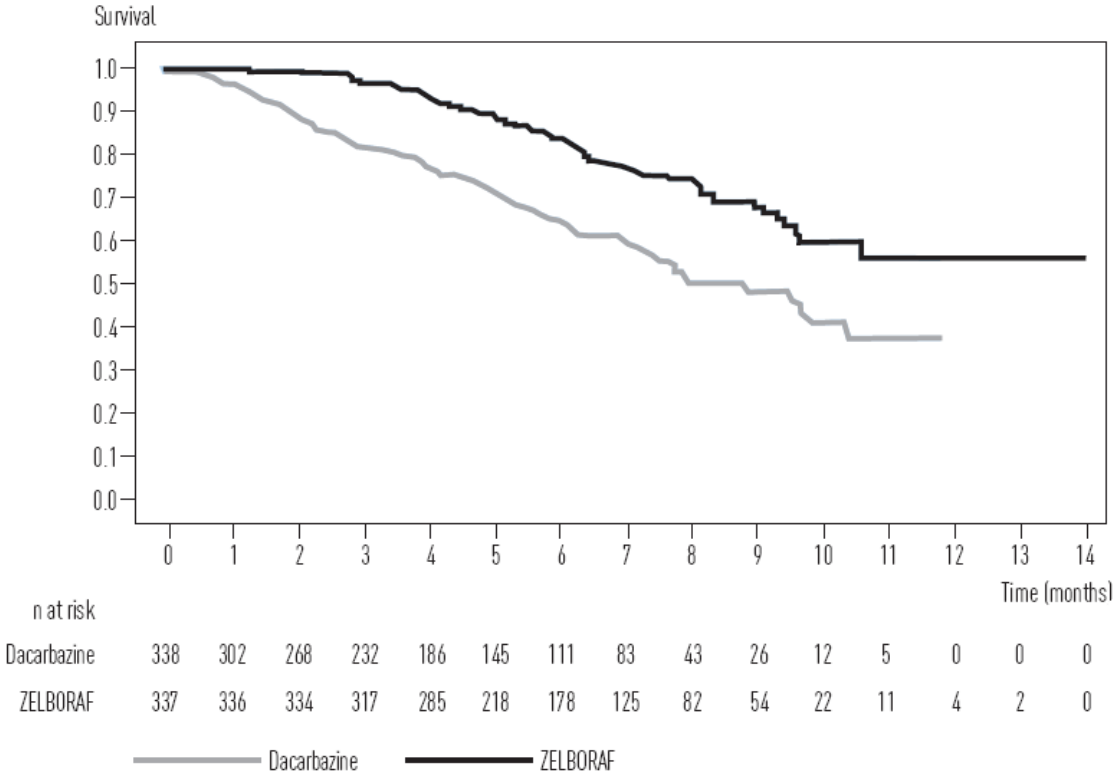
[a] As detected by the cobas® 4800 BRAF V600 Mutation Test

[b] Hazard ratio estimated using Cox model; a hazard ratio of < 1 favors ZELBORAF

[c] Kaplan-Meier estimate

[d] Unstratified log-rank test

Figure 1 Kaplan-Meier Curves of Overall Survival – Treatment Naive Patients



The confirmed, investigator-assessed best overall response rate was 48.4% (95% CI: 41.6%, 55.2%) in the ZELBORAF arm compared to 5.5% (95% CI: 2.8%, 9.3%) in the dacarbazine arm. There were 2 complete responses (0.9%) and 104 partial responses (47.4%) in the ZELBORAF arm and all 12 responses were partial responses (5.5%) in the dacarbazine arm.

A single-arm, multicenter, multinational trial (Trial 2) was conducted in 132 patients with $BRAF^{V600E}$ mutation-positive metastatic melanoma, as detected by the cobas® 4800 BRAF V600 Mutation Test, who had received at least one prior systemic therapy. The median age was 52 years with 19% of patients being older than 65 years. The majority of patients were male (61%) and Caucasian (99%). Forty-nine percent of patients received ≥ 2 prior therapies. The median duration of follow-up was 6.87 months (range, 0.6 to 11.3).

The confirmed best overall response rate as assessed by an independent review committee (IRC) was 52% (95% CI: 43%, 61%). There were 3 complete responses (2.3%) and 66 partial responses (50.0%). The median time to response was 1.4 months with 75% of responses occurring by month 1.6 of treatment. The median duration of response by IRC was 6.5 months (95% CI: 5.6, not reached).

ZELBORAF has not been studied in patients with wild-type BRAF melanoma.

8. Safety

The following summary of adverse reactions is from the agreed upon package insert.

The adverse drug reactions (ADRs) described in this section were identified from Trial 1 and Trial 2 *[see Clinical Studies (14)]*. In Trial 1, treatment naive patients with unresectable or metastatic melanoma (n=675) were allocated to ZELBORAF 960 mg orally twice daily or to dacarbazine 1000 mg/m^2 intravenously every 3 weeks. In Trial 2, (n=132) patients with metastatic melanoma and failure of at least one prior systemic therapy received treatment with ZELBORAF 960 mg orally twice daily. Adverse reactions reported in at least 10% of patients treated with ZELBORAF are presented in

Table 2. The most common adverse reactions of any grade (≥ 30% in either study) reported in ZELBORAF-treated patients were arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus and skin papilloma. The most common (≥ 5%) Grade 3 adverse reactions were cuSCC and rash. The incidence of Grade 4 adverse reactions was ≤ 4% in both studies.

The incidence of adverse events resulting in permanent discontinuation of study medication in Trial 1 was 7% for the ZELBORAF arm and 4% for the dacarbazine arm. In Trial 2, the incidence of adverse events resulting in permanent discontinuation of study medication was 3% in ZELBORAF-treated patients. The median duration of study treatment was 4.2 months for ZELBORAF and 0.8 months for dacarbazine in Trial 1, and 5.7 months for ZELBORAF in Trial 2.

Table 2 Adverse Reactions Reported in ≥ 10% of Patients Treated with ZELBORAF*

ADRs	Trial 1: Treatment Naive Patients						Trial 2: Patients with Failure of at Least One Prior Systemic Therapy		
	ZELBORAF n= 336			Dacarbazine n= 287			ZELBORAF n= 132		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Skin and subcutaneous tissue disorders									
Rash	37	8	-	2	-	-	52	7	-
Photosensitivity reaction	33	3	-	4	-	-	49	3	-
Alopecia	45	<1	-	2	-	-	36	-	-
Pruritus	23	1	-	1	-	-	30	2	-
Hyperkeratosis	24	1	-	<1	-	-	28	-	-
Rash maculo-papular	9	2	-	<1	-	-	21	6	-
Actinic keratosis	8	-	-	3	-	-	17	-	-
Dry skin	19	-	-	1	-	-	16	-	-
Rash papular	5	<1	-	-	-	-	13	-	-
Erythema	14	-	-	2	-	-	8	-	-
Musculoskeletal and connective tissue disorders									
Arthralgia	53	4	-	3	<1	-	67	8	-
Myalgia	13	<1	-	1	-	-	24	<1	-
Pain in extremity	18	<1	-	6	2	-	9	-	-
Musculoskeletal pain	8	-	-	4	<1	-	11	-	-
Back pain	8	<1	-	5	<1	-	11	<1	-
General disorders and administration site conditions									
Fatigue	38	2	-	33	2	-	54	4	-
Edema peripheral	17	<1	-	5	-	-	23	-	-
Pyrexia	19	<1	-	9	<1	-	17	2	-
Asthenia	11	<1	-	9	<1	-	2	-	-
Gastrointestinal disorders									
Nausea	35	2	-	43	2	-	37	2	-
Diarrhea	28	<1	-	13	<1	-	29	<1	-
Vomiting	18	1	-	26	1	-	26	2	-
Constipation	12	<1	-	24	-	-	16	-	-
Nervous system disorders									
Headache	23	<1	-	10	-	-	27	-	-
Dysgeusia	14	-	-	3	-	-	11	-	-
Neoplasms benign, malignant and unspecified (includes cysts and polyps)									
Skin papilloma	21	<1	-	-	-	-	30	-	-
Cutaneous SCC[†#]	24	22	-	<1	<1	-	24	24	-
Seborrheic keratosis	10	<1	-	1	-	-	14	-	-

ADRs	Trial 1: Treatment Naive Patients						Trial 2: Patients with Failure of at Least One Prior Systemic Therapy		
	ZELBORAF n= 336			Dacarbazine n= 287			ZELBORAF n= 132		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Investigations Gamma-glutamyltransferase increased	5	3	<1	1	-	-	15	6	4
Metabolism and nutrition disorders Decreased appetite	18	-	-	8	<1	-	21	-	-
Respiratory, thoracic and mediastinal disorders Cough	8	-	-	7	-	-	12	-	-
Injury, poisoning and procedural complications Sunburn	10	-	-	-	-	-	14	-	-

*Adverse drug reactions, reported using MedDRA and graded using NCI-CTC-AE v 4.0 (NCI common toxicity criteria) for assessment of toxicity.

† Includes both squamous cell carcinoma of the skin and keratoacanthoma.

All cases of cutaneous squamous cell carcinoma were to be reported as Grade 3 per instructions to study investigators and no dose modification or interruption was required.

Clinically relevant adverse events reported in < 10% of patients treated with vemurafenib in the phase 2 and 3 trials include erythrodysaesthesia syndrome, keratosis pilaris, erythema nodosum, Stevens-Johnson syndrome, arthritis, dizziness, peripheral neuropathy, VIIth nerve paralysis, basal cell carcinoma, folliculitis, weight loss, retinal vein occlusion, uveitis, vasculitis, and atrial fibrillation.

The incidence of worsening liver laboratory abnormalities in the randomized trial are shown in Table 3 from the package insert as the proportion of patients who experienced a shift from baseline to Grade 3 or 4.

Table 3 Change From Baseline to Grade 3/4 Liver Laboratory Abnormalities*

Parameter	Change From Baseline to Grade 3/4	
	ZELBORAF (%)	Dacarbazine (%)
GGT	11.5	8.6
AST	0.9	0.4
ALT	2.8	1.9
Alkaline phosphatase	2.9	0.4
Bilirubin	1.9	-

* For ALT, alkaline phosphatase and bilirubin, there were no patients with a change to grade 4 in either treatment arm.

Safety issues that are addressed in the Warnings and Precautions section of the package insert include cutaneous squamous cell carcinomas, serious hypersensitivity reaction, Stevens-Johnson syndrome and toxic epidermal necrolysis, QT-prolongation, liver laboratory abnormalities, photosensitivity, uveitis and other ophthalmologic reactions, new primary malignant melanomas, and pregnancy category D.

The cutaneous squamous cell carcinomas (cuSCC) included both SCCs of the skin and keratoacanthomas. The incidence of cuSCC in vemurafenib-treated patients in the randomized trial was 24%. They usually occurred early in the course of treatment and the median time to the first appearance of 7 to 8 weeks. Approximately 33% of patients with cuSCC experienced greater than one occurrence with median time between occurrences of 6 weeks. The cuSCC's were managed with excision and patients were able to continue treatment without dose adjustment.

9. Advisory Committee Meeting

The application was not referred to an FDA advisory committee because the benefit/risk profile of Zelboraf (vemurafenib) Tablet is clearly favorable for the proposed indication.

10. Pediatrics

Vemurafenib is exempt from the requirement for pediatric studies because of orphan drug designation.

11. Other Relevant Regulatory Issues

The DSI audits and financial disclosures are addressed the following excerpt from the CDTL Review.

> In the clinical inspection summary dated July 28, 2011, the Office of Scientific Investigations (OSI) considered the submitted clinical data reliable except for the identification of incomplete radiographic data documentation and irreproducible target lesion assessments at Study Site 201192, one of four study sites inspected for this NDA. This finding was based on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations. OSI recommended the review division consider the impact of this finding on the disease progression endpoint assessment.
>
> To assess the effect of the reported radiographic data violations on the co-primary endpoint, a reanalysis of PFS was conducted with exclusion of all patients from Study Site 201192. The reanalysis showed no changes in the PFS results compared to the

ITT-based PFS analysis. (See the clinical review and statistical review addendum for details).

The financial disclosures were evaluated by the primary reviewer and found acceptable.

There are no unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: The proprietary name ZELBORAF was found to be acceptable.
- Physician labeling: Agreement has been reached on the physician labeling. The final indication reflects the population studied.

  ZELBORAF™ is indicated for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation as detected by an FDA-approved test.

  Limitation of Use: ZELBORAF is not recommended for use in patients with wild-type BRAF melanoma.
- Carton and immediate container labels: Agreement has been reached on carton and container labels.
- Patient labeling/Medication guide: Agreement has been reached on the MedGuide.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval
- Risk Benefit Assessment

  The risk benefit assessment is clearly favorable for the proposed population. Until the approval of ipilimumab earlier this year, no treatment had been shown to improve overall survival in advanced malignant melanoma. Although the median survival has not yet been reached for vemurafenib in the randomized study, the overall survival in the vemurafenib arm is clearly superior to that in the dacarbazine arm. Additional follow-up will provide a better estimate of the survival with vemurafenib treatment. The improvement in survival is supported by clinically and statistically significant improvements in progression-free survival and objective response rate. The toxicity

profile is better than that of most cytotoxic chemotherapeutic agents and is clearly acceptable for a disease that has a dismal prognosis. The Clinical and CDTL Reviews also found the risk benefit profile to be favorable.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  Routine post-marketing surveillance is recommended.

- Recommendation for other Postmarketing Requirements and Commitments:

  Post-marketing requirements:

  In order to identify unexpected serious risks from the effects of inhibition human CYP2C8 and CYP2B6 by vemurafenib the following study is required:

1803-1 Perform an *in vitro* screen to determine if vemurafenib is an inhibitor of human CYP2C8 and CYP2B6. Based on results from the *in vitro* screen, a clinical drug-drug interaction trial may be needed.

In order to identify unexpected serious risks from longer duration of exposure to vemurafenib, an increase in secondary malignancies with vemurafenib, drug-drug interactions with vemurafenib, and the effect of severe hepatic impairment on the pharmacokinetics of vemurafenib the following clinical trials are required.

1803-2 Submit the final analysis of safety in the ongoing trial (Protocol NO25026:BRIM3) to provide the potential for new safety signals from longer duration of exposure.

1803-3 Submit an analysis of secondary malignancies for the proposed adjuvant melanoma trial [G027826: Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Vemurafenib (RO5185426) Adjuvant Therapy in Patients with Surgically-Resected, Cutaneous BRAF Mutant Melanoma at High Risk for Recurrence] annually and one year after the last patient has completed clinical trial treatment.

1803-4 Follow-up for secondary malignancies from the planned papillary thyroid cancer trial [N025530: An Open-Label, Multi-Center Phase II Study of the BRAF Inhibitor RO5185426 in Patients with Metastatic or Unresectable Papillary Thyroid Cancer (PTC) positive for the BRAF V600 Mutation and Resistant to Radioactive Iodine] annually and one year after the last patient has completed clinical trial treatment.

1803-5 Conduct a drug interaction trial to evaluate the effect of a strong CYP3A inducer (e.g., rifampin) on the pharmacokinetics of vemurafenib.

1803-6 Conduct a drug interaction trial to evaluate the effect of a strong CYP3A4 inhibitor (e.g., ketoconazole) on the pharmacokinetics of vemurafenib.

1803-7 Conduct a clinical trial in patients with normal hepatic function and patients with pre-existing severe hepatic impairment to assess the effect of severe hepatic impairment on the pharmacokinetics of vemurafenib.

Post-marketing commitments:

The following post-marketing commitment is intended to provide a better estimate of survival with vemurafenib treatment.

1803-8 Submit updated overall survival results from the ongoing trial (Protocol NO25026:BRIM3) with a minimum follow-up of 24 months after the last patient was enrolled into the trial.

The following PMC is intended to evaluate the activity of vemurafenib in patients with unresectable or metastatic malignant melanoma with the V600K BRAF mutation because some of the patients enrolled on the BRIM3 trial were identified by the cobas® 4800 V600 Mutation Test as having the V600E mutation but were found to have the V600K mutation by Sanger sequencing.

1803-9 Develop an Investigational Use Only, Companion Diagnostic (IUO CoDx) that reliably detects V600K BRAF mutation in patients with unresectable or metastatic melanoma and conduct an open-label single arm trial with overall response rate and duration of response as the primary endpoints in this population as determined by the diagnostic test.

The following PMC is intended to determine whether NRAS mutation plays a role in disease progression in patients with the V600E BRAF mutation who have been treated with vemurafenib.

1803-10 Assess changes in NRAS mutation status at both baseline and disease progression in biopsy accessible lesions in patients with advanced melanoma positive for the V600E BRAF mutation who have been treated with vemurafenib. This assessment should include all patients with available biopsy specimens and may be derived from completed and ongoing trials [see below for trial ID number and title*] in patients treated with vemurafenib.

*PLX06-02: A Study to Assess Safety, Pharmacokinetics, and Pharmacodynamics of PLX4032 in Patients with Solid Tumors
*NP22657: An Open-Label, Multi-Center, Phase II Study of Continuous Oral Dosing of RO5185426 in Previously Treated Patients With Metastatic Melanoma
*NO25026: A Randomized, Open-label, Controlled, Multicenter, Phase III Study in Previously Untreated Patients With Unresectable Stage IIIC or Stage IV

Melanoma with V600E BRAF Mutation Receiving RO5185426 or Dacarbazine

*NP25163: A Phase I, Randomized, Open-label, Multi-center, Multiple Dose Study to Investigate the Pharmacokinetics and Pharmacodynamics of RO5185426 Administered as 240 mg Tablets to Previously Treated BRAF V600E Positive Metastatic Melanoma Patients

*NP25396: A Phase I, Randomized, Open-label, Multi-center, Two Period Crossover Study to Investigate the Effect of Food on the Pharmacokinetics of a Single Oral Dose of RO5185426, Followed by Administration of 960 mg RO5185426 Twice Daily to $BRAF^{V600E}$ Positive Metastatic Melanoma Patients