CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202429Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	July 22, 2011
To:	Robert Justice, M.D., Director Division of Drug Oncology Products
Through:	Mary Willy, Ph.D., Deputy Director Division of Risk Management (DRISK)
From:	Joyce Weaver, Pharm.D., Senior Risk Management Analyst (RMA), DRISK Cynthia LaCivita, Pharm.D., RMA Team Leader, DRISK
Subject:	Risk Management Plan submission of April 27, 2011
Drug Name (Established Name):	Vemurafenib (Zelboraf) tablets
Therapeutic Class:	Kinase inhibitor
Dose and Route:	960 mg orally twice daily
Application Type/Number:	NDA 202429
Applicant:	Hoffman-La Roche
OSE RCM #:	2011-1491

1 INTRODUCTION

Vemurafenib is a BRAF serinethreonine kinase inhibitor formulated as a 240-mg film-coated tablet. The proposed indication for vemurafenib is for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma. The risk management plan submitted with the application proposes routine risk management activities, labeling and routine pharmacovigilance; the sponsor did not propose a REMS for vemurafenib.

2 MATERIAL REVIEWED

- Risk Management Plan submission of April 27, 2011.
- Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507-2516.
- American Cancer Society, Melanoma Overview. http://www.cancer.org/acs/groups/cid/documents/webcontent/003063-pdf.pdf. Accessed July 18, 2011.
- The Skin Cancer Foundation-Skin Cancer Facts. http://www.skincancer.org/Skin-Cancer-Facts. Accessed July 18, 2011.
- Jerant AF, Johnson JT, Sheridan CD, Caffrey TJ. Early detection and treatment of skin cancer. *Am Fam Physician* 2000; **62**: 357–368, 375–376, 381–382.
- Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Research Data (1973-2008), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2011, based on the November 2010 submission.
- Draft vemurafenib clinical safety review, Amy McKee, MD.

3 RESULTS OF REVIEW

3.1 Efficacy

The efficacy of vemurafenib was tested in a randomized clinical trial that compared vemurafenib to dacarbazine in patients with previously untreated, metastatic melanoma with the BRAF V600 mutation. The 675 patients in the trial were selected for the study from over 2,000 patients screened for inclusion in the study. Most of the patients excluded from the study were excluded because the patients' melanomas lacked the BRAF C600 mutation. Patients in the trial received either vemurafenib (960 mg orally twice daily) or dacarbazine (1000 mg per meter squared of body surface area, intravenously every 3 weeks). Primary end points were rates of overall and progression-free survival.

At 6 months, overall survival was 84% (95% confidence interval [CI], 78-89) in the patients receiving vemurafenib and 64% (95% CI, 56-73) in the patients receiving dacarbazine. In the interim analysis for overall survival vemurafenib was associated with a relative reduction of 63% in the risk of death (P<0.001) as compared with

dacarbazine. In the analysis for death or progression-free survival, vemurafenib was associated with a relative reduction of 74% in the risk (P<0.001), as compared with dacarbazine.

After review of the interim results by a data and safety monitoring board, the board recommended that study patients in the dacarbazine arm be treated with vemurafenib.

3.2 Safety

Common adverse events associated with vemurafenib were arthralgia, rash, fatigue, alopecia, keratoacanthoma or squamous-cell carcinoma, photosensitivity, nausea, and diarrhea. The sponsor analyzed seven risks from the vemurafenib clinical trials for the level of risk mitigation needed. These risks include cutaneous squamous cell carcinoma (cuSCC), QT-prolongation, liver test abnormalities, photosensitivity, rash, arthralgia, and fatigue. The sponsor believes that all the risks can be managed with appropriate labeling and routine pharmacovigilance.

In a preliminary assessment of safety data, photosensitivity, rash, arthralgia, and fatigue were not noted as concerning by the FDA Medical Officer reviewing the safety of vemurafenib. The FDA Interdisciplinary Review Team-QT Consult group (IRT-QT) review of the QT-prolonging effects of vemurafenib indicated that only minor labeling was needed to address this issue.

In clinical testing, there were 79 instances of keratoacanthomas and cuSCCs in vemurafenib-treated patients (24%) compared to one (< 1%) in the dacarbazine-treated patients. The median time to onset was 7.1 weeks. No cases were reported after 28 days off treatment. Some patients had multiple lesions, with six patients having five or more lesions. Treatment was not interrupted because of the lesions, and most (60/62) were managed with excision (the management and outcome of the other two lesions were not reported). Seven patients developed new lesions identified as melanoma. The lesions were excised, and treatment continued.

The sponsor proposes including information about cuSCC in the *Warnings and Precautions* section of the labeling. They propose routine pharmacovigilance to monitor this event in the postmarketing period.

Additionally, the sponsor has proposed conducting an epidemiology study in the (b) (4) database to examine the incidence of cuSCC in (b) (4) members diagnosed with melanoma.

4 DISCUSSION

The sponsor believes that appropriate product labeling about the risk of secondary skin lesions, including cuSCC, will be sufficient to accomplish appropriate monitoring of patients for cuSCC. The labeling for vemurafenib will contain a prominent warning about this risk.

The Food and Drug Administration Amendments Act (FDAAA) of 2007 requires that the Agency consider six factors in determining whether a REMS is needed for a given product. These factors are: the estimated size of the population likely to use the drug involved, the seriousness of the disease or condition that is to be treated with the drug, the expected benefit of the drug with respect to such disease or condition, the expected or actual duration of treatment with the drug, the seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug, and whether the drug is a new molecular entity. After considering these factors, a REMS should be instituted for a product if the REMS is needed to ensure that the benefits of the product outweigh its risks.

The data for the six factors for vemurafenib are detailed below. The only adverse event under consideration for mitigation via a REMS is cuSCC.

- The estimated size of the population likely to use the drug involved.
    - The American Cancer Society estimates that about 70,230 new cases of melanoma will occur in the United States in 2011. Of these, 36-54% (25,280-39,000) will have the BRAF V600 mutation. The population eligible to receive vemurafenib will be further reduced because only a subsection of melanomas present either as advanced disease, or ultimately proceed to advanced disease. About 16% of melanomas, representing about 4,050-6240 cases, are advanced when the melanoma is diagnosed (NCI SEER data). Some additional cases will progress to advanced disease after diagnosis.

- The seriousness of the disease or condition that is to be treated with the drug.
    - The American Cancer Society estimates that 8,790 patients will die from melanoma in the United States in 2011.

- The expected benefit of the drug with respect to such disease or condition.
    - Vemurafenib was associated with a relative reduction of 63% in the risk of death, and a relative reduction of 74% in the risk of tumor progression in the study subjects, as compared to dacarbazine.

- The expected or actual duration of treatment with the drug.
    - Patients are treated with vemurafenib until disease progression or unacceptable toxicity occurs.

- The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
    - SCC is the second most common form of skin cancer in the US, with an estimated 700,000 cases diagnosed each year. Most cuSCCs are successfully treated with surgical excision, with 2-6% risk of metastasis (Jerant et al).

- Whether the drug is a new molecular entity (NME).
    - Vemurafenib is an NME.

It appears that the benefits of vemurafenib likely outweigh its risks. Although monitoring patients taking vemurafenib for new skin lesions is needed for the optimum use of vemurafenib, the benefits of vemurafenib in reducing the risk of death and in reducing tumor progression would likely outweigh its risks even if monitoring for new skin lesions were conducted in an irregular manner.

5 CONCLUSION AND RECOMMENDATION

The decision to forego a REMS at this time is reasonable based on the risk-benefit profile of vemurafenib and the narrow population eligible for treatment with vemurafenib. Should postmarketing data show that vemurafenib prescribers are not monitoring their patients for cuSCCs, and, consequently, diagnoses of cuSCCs are being delayed with significant sequelae for patients, the need for a REMS to mitigate this risk can be revisited.

We defer to the Division of Epidemiology (DEPI) for an assessment of the utility of the proposed epidemiology study.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOYCE P WEAVER
07/22/2011

MARY E WILLY
07/22/2011
I concur