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RESEARCH**

APPLICATION NUMBER:

202429Orig1s016

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Edvardas Kaminskas, M.D.
Subject	Deputy Division Director Summary Review
NDA #	202429
Supplement #	016
Applicant Name	Hoffmann-LaRoche, Inc./Genentech, Inc.
Date of Submission	6/7/2017
PDUFA Goal Date	12/7/2017
Proprietary Name / Established (USAN) Name	Zelboraf® Vemurafenib
Dosage Forms / Strength	Tablets 240 mg
Proposed Indications	Treatment of patients with Erdheim Chester Disease (ECD) with BRAF 600 mutation
Action:	Regular Approval

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Patricia Oneal, M.D./Virginia Kwitkowski, M.S., ACNP-BC
Statistical Review	Lola Luo, Ph.D./Yuan-Li Shen, Ph.D./Thomas E. Gwise, Ph.D.
Clinical Pharmacology Review	Sriram Subramaniam, Ph.D./Stacy Shord, Pharm.D./Bahru Habtemariam, Pharm.D.
OSI/DCCE/GCPAB	Min Lu, M.D., M.P.H./Janice Pohlman, M.D., M.P.H./Kassa Ayalew, M.D., M.P.H.
CDTL Review	Virginia Kwitkowski, M.S., ACNP-BC
OSE/DMEPA/OMEPRM	Nicole Garrison, Pharm.D./Hina Mehta, Pharm.D.
OMP/DMPP	LaShawn Griffiths, MSHS-PH/Sharon R. Mills, BSN/Ruth Lidoshore, Pharm.D.
OSE/OPDP	Nicholas Senior, Pharm.D., J.D.
RPM	Jennifer J. Lee, Pharm.D.

OND=Office of New Drugs
 OSE= Office of Surveillance and Epidemiology
 OMEPRM=Office of Medication Error Prevention and Risk Management
 DMEPA=Division of Medication Error Prevention and Analysis
 OMP/DMPP=Office of Medical Policy/Division of Medical Policy Programs
 OPDP=Office of Prescription Drug Promotion
 OSI= Office of Scientific Investigations
 DCCE/GCPAB=Division of Clinical Compliance Evaluation/Good Clinical Practice Assessment Branch
 CDTL=Cross-Discipline Team Leader
 RPM=Regulatory Project Manager

Signatory Authority Review Template

1. Introduction

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis affecting adults between their 5th and 7th decades of life, with slight male predominance. Approximately 600 to 700 cases have been reported since the initial description of the disease in 1930. The etiology of the disease is unknown and there is no evidence that ECD is an inheritable genetic disorder. Presentation of the disease is very variable, with neurological, skeletal, endocrine, cardiac and pulmonary symptomatology most prominent. The diagnosis is made by the distinct histological pattern of non-Langerhans foamy histiocytes positive for CD68, CD163, and Factor XIIIa infiltrating various organs, along with radiological and clinical findings. Currently, there are no accepted guidelines for the diagnosis and treatment of ECD. There are no FDA-approved drugs or biologics. Steroids, cytotoxic agents and autologous hematopoietic stem cell transplantation were used until interferon-alpha, interleukin 1, cladribine, infliximab were reported as efficacious. BRAF inhibitor vemurafenib was reported as effective in patients with ECD with a BRAF V600E mutation, which has been found in approximately half of the reported cases. The availability of several drugs selectively inhibiting BRAF or its downstream kinases could represent potential therapies for severe forms of ECD.

2. Background

Zelboraf (vemurafenib) was first approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test on August 17, 2011. It has since been approved in 102 countries (as of May 3, 2017).

Starting in 2014, the Applicant had a number of meetings with the Agency regarding development of vemurafenib for treatment of (b) (4) BRAF V600E mutation, (b) (4), ECD, (b) (4). Orphan drug designation was granted for the treatment of ECD on August 2, 2016. IND for this indication was submitted in October, 2016. Breakthrough Therapy designation was granted in April, 2017.

3. CMC/Device

There was no new CMC information submitted in this application.

4. Nonclinical Pharmacology/Toxicology

There was no new nonclinical pharmacology/toxicology information submitted in this application.

5. Clinical Pharmacology/Biopharmaceutics

“The Office of Clinical Pharmacology/Division of Clinical Pharmacology V reviewed the information contained in supplement 16. The supplement is approvable from a clinical pharmacology perspective...The recommended dose of 960 mg BID, with or without food is supported by the limited PK data that indicates that the PK is similar for patients with different diseases. No E-R can be explored in the ECD population, as PK samples were only collected from one patient with ECD.”

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A.

7. Clinical/Statistical-Efficacy

To support the proposed indication, the Applicant conducted one Phase II study entitled “MO28072. An open-label, multicenter, multinational Phase II study exploring the efficacy and safety of vemurafenib in a diverse population of patients with cancers known to harbor BRAF V600 mutations and for whom vemurafenib is deemed the best option in the opinion of the investigator.” A total of 208 patients were enrolled in 7 cohorts (NSCLC, ovarian, colorectal, cholangiocarcinoma, breast, multiple myeloma, and other solid tumors). Among the patients with “other solid tumors” were 22 patients with ECD. All patients were treated with 960 mg of vemurafenib orally every 12 hours. The primary efficacy endpoint was ORR (Overall Response Rate) assessed by Investigator using RESIST v.1.1 criteria. Responses were defined as complete response (CR) and partial response (PR) as determined on two occasions ≥ 4 weeks apart as assessed by the investigator. Key secondary endpoints were PFS, TTP, best response, clinical benefit rate, time to response, duration of response, and overall survival.

The median age of subjects was 58.5 years (range, (b) (6) years), male/female ratio was (b) (6) %, (b) (6) %, ECOG status was 0 in 18%, 1 in 55%, and 2 in 23%. Prior systemic therapies were as follows: one in 32%, two in 23%, three or more in 14%, none in 32% of patients.

At the time of sNDA submission all study subjects with ECD were no longer receiving study treatment and all had discontinued from the study. The reasons for discontinuation from the study were an adverse event (in 32% of subjects), withdrawal by subject (in 23%), physician

decision (in 5%) and other reasons (in 41%). The median time to study discontinuation was 26.6 months (range 3.1 – 44.3 months); the median time to discontinuation of vemurafenib was 14.2 months (range, 1.6 – 44.2 months).

The efficacy results are shown below in Clinical Reviewer's Table 7. One subject had a complete response (CR) and 11 subjects had a partial response (PR) for ORR of 54.5%. The median time to response was 11.0 months (range (3.7 – 14.6 months). Other secondary endpoints were not evaluable.

Table 7 Overall Response Rate by Investigator (ECD Cohort MO28072)

Efficacy Result	ECD patients (N=22)
Median duration of follow-up (months) (Min, Max)	26.64 (3.0, 44.3)
ORR by Investigator (95% CI)	12 (54.5%) (32.21, 75.61)
Complete response	1 (4.5%)
Partial response	11 (50.0%)
Stable disease	9 (40.9%)
Progressive disease	0
Not Measurable	1 (4.5%)

The Applicant provided efficacy narratives for all study subjects. These are illuminating, because of the great variety organ systems involved and consequently different symptomatology.

It should be noted that all subjects had at least one dose reduction and one dose interruption due to adverse reaction (AR). These data are shown in Reviewer's Tables 11 and 12 below. The most common ARs leading to dose reduction or interruption in subjects with ECD were maculopapular rash, fatigue, arthralgia, palmar-plantar erythrodysesthesia, and increased lipase. More subjects with ECD required dose reduction or interruption than patients with non-small cell lung cancer or metastatic melanoma. These dose reductions and interruptions did not appear to affect the tumor response rate (ORR was 38% in 8 subjects treated with 720 mg BID and 64% in 14 subjects treated with 480 mg BID).

Table 11 Patients (%) with at least one dose reduction (DR) due to adverse reactions

Disease (n)	DR to 720 mg	DR to 480 mg	DR to 240 mg
ECD (n=22)	91%	64%*	0
NSCLC (n=62)	53%	16%	3%
MM (n=3219) †	19%	6%	<0.5%

*includes 2 patients with DR from 960 to 480 mg † Table 27, Study MO25515

ECD and NSCLC results based on analysis of dataset aex.xpt

ECD= Erdheim-Chester Disease, NSCLC=non-small cell lung cancer, MM=metastatic melanoma

Table 12 Patients (%) with at least one dose interruption (DI) due to adverse reactions

Disease (n)	1 DI	2 DI	≥3 DI
ECD (n=22)	32%	36%	32%
NSCLC (n=62)	37%	21%	8%
MM (n=3219) †	28%	13%	NA

† Table 28, Study MO25515. NA=not available

ECD and NSCLC results based on analysis of dataset aex.xpt

ECD= Erdheim-Chester Disease, NSCLC=non-small cell lung cancer, MM=metastatic melanoma

8. Safety

Safety was evaluated in Study MO28072 and Study MO25515, an open label, non-randomized study of safety and tolerability of vemurafenib in 3224 patients with BRAF V600-positive malignant melanoma. The Applicant compared the incidence of the most common treatment-emergent adverse events between subjects with ECD and non-ECD as well as with subjects with metastatic melanoma in the Study MO25515 database. This analysis was problematic because of the small sample size of subjects with ECD; however, both studies share similar patterns of clinically relevant adverse events.

Non-fatal serious adverse events occurred in 73% of subjects with ECD. There were no Grade 5 SAEs. Four subjects had an SAE that led to withdrawal from treatment (15%) and seven subjects had an SAE that led to dose modification or interruption (27%). Among the significant adverse events were cutaneous squamous cell carcinoma, liver enzyme elevations, and both myelodysplasia and chronic myelomonocytic leukemia (1 subject).

All subjects with ECD had at least one AE. The most common were arthralgia (86%), maculopapular rash (68%), alopecia (73%), fatigue (68%), QT prolongation (64%), skin papilloma (55%), hyperkeratosis (68%), and diarrhea (50%).

There were no new safety signals in subjects with ECD.

9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

10. Pediatrics

Vemurafenib was granted Orphan Drug Designation for treatment of ECD and the Applicant is exempt from performing Pediatric studies.

11. Other Relevant Regulatory Issues

Office of Clinical Investigations inspected one clinical site and issued a Voluntary Action Indicated classification due to failure to promptly report some non-serious adverse events and document all concomitant medications. The inspector concluded that “these observations appear unlikely to have significant impact on the overall efficacy and safety of the study. In general, this clinical site appeared to be in compliance with Good Clinical Practices except for the above observation.”

There are no other unresolved relevant regulatory issues.

12. Labeling

Physician labeling and Patient labeling/Medication guide were reviewed by reviewers in DMEPA and DMPP.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Regular Approval.
- Risk Benefit Assessment: Treatment of patients with ECD with BRAF V600 mutation with vemurafenib resulted in objective response rate of 54%. The improvement in disease-related symptoms and physical function was also documented in 15 of 22 patients and supports the clinical benefit of using vemurafenib in patients with ECD. Several safety signals including cutaneous malignancies, hypertension, QT prolongation and infection require appropriate monitoring and management, but do not outweigh the overall clinical benefit. Vemurafenib has a favorable benefit/risk evaluation for patients with ECD.

- Recommendation for Postmarketing Risk Management Activities: None.
- Recommendation for other Postmarketing Study Commitments: None.

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/s/

EDVARDAS KAMINSKAS
11/05/2017