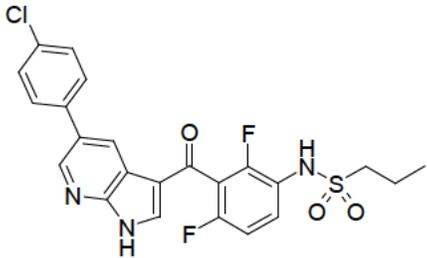


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202429Orig1s016**

**PRODUCT QUALITY REVIEW(S)**

<b>CHEMISTRY REVIEW</b> Filing Review	<b>1. ORGANIZATION</b> OPQ/OLDP/DPMA I/Branch I	<b>2. NDA NUMBER</b> N202429 (Approved 17-Aug-2011)
<b>3. NAME AND ADDRESS OF APPLICANT</b> Hoffmann-La Roche, Inc. c/o Genentech (wholly owned subsidiary of Hoffmann-La Roche, Inc.) 1 DNA Way South San Francisco, CA 94080		<b>4. SUPPLEMENT NUMBER, DATE</b> N202429/S-016, 06-Jun-2017
<b>5. PROPRIETARY NAME</b> Zelboraf®	<b>6. NAME OF THE DRUG</b> Vemurafenib	<b>7. AMENDMENTS, REPORT, DATE</b> N202429/S-016, 12-Jul-2017
<b>8. SUPPLEMENT PROVIDES INFORMATION FOR</b> Efficacy supplement based on IND 121566 under co-development with Plexxikon Inc. for the treatment of patients with Erdheim-Chester Disease (ECD) containing BRAF V600 mutation.		
<b>9. PHARMACOLOGICAL CATEGORY</b> Anti-neoplastic, kinase inhibitor	<b>10. HOW DISPENSED</b> Rx	<b>11. RELATED IND, NDA, DMF</b>
<b>12. DOSAGE FORM</b> Oral Tablets	<b>13. POTENCY</b> 240 mg	
<b>14. CHEMICAL NAME AND STRUCTURE</b>		
<p style="text-align: center;"><b><u>Zelboraf (vemurafenib)</u></b></p>  <p style="text-align: center;">propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide Molecular formula: C<sub>23</sub>H<sub>18</sub>ClF<sub>2</sub>N<sub>3</sub>O<sub>3</sub>S Molecular weight: 489.9</p>		<p>Each tablet of Zelboraf contains 240 mg of vemurafenib. Inactive ingredients in <b>Tablet core</b>: hypromellose acetate succinate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, and hydroxypropyl cellulose. <b>Coating</b>: pinkish white: poly (vinyl alcohol), titanium dioxide, polyethylene glycol 3350, talc, and iron oxide red.</p> <p>Vemurafenib is an 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.</p>
<b>15. COMMENTS</b>		
<p>Zelboraf is approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. <u>ZELBORAF is not indicated for treatment of patients with wild-type BRAF melanoma.</u></p> <p>The subject efficacy supplement proposes for the treatment with Zelboraf of patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation based on IND 121566 under co-development with Plexxikon Inc. <u>Zelboraf is not indicated for treatment of patients with wild-type BRAF ECD.</u></p> <p>There were no CMC related changes submitted for review. The CMC related Sections in the proposed PI namely, Dosage Forms and Strengths, Description, and How Supplied/Storage and Handling had no changes made.</p> <p>The applicant submitted a claim for categorical exclusion from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(b). The request for categorical exclusion may be granted.</p>		

<b>16. CONCLUSION AND RECOMMENDATION</b>		
There were no CMC related changes submitted for review in the subject efficacy supplement. The supplement as amended is Fileable from the CMC review perspective.		
<b>17. NAME</b>	<b>18. REVIEWERS SIGNATURE</b>	<b>19. DATE COMPLETED</b>
Pallaiah Thammana	See electronic signature sheet	25-Jul-2017
<b>DISTRIBUTION: ORIGINAL JACKET    CSO    REVIEWER    DIVISION FILE</b>		
<b>DHP</b>		

AP



Ramesh  
Raghavachari

Digitally signed by Ramesh Raghavachari  
Date: 7/26/2017 04:05:08PM  
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Pallaiah  
Thammana

Digitally signed by Pallaiah Thammana  
Date: 7/26/2017 05:40:51PM  
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