CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202429Orig1s000

CHEMISTRY REVIEW(S)

NDA 202-429

Zelboraf (vemurafenib) film-coated tablets

Hoffman-La Roche, Inc.

Anne Marie Russell, Ph.D.
Review Chemist

Office of New Drug Quality Assessment
Division I Branch II
for
The Division of Drug Oncology Products

1. NDA 202-429
2. CMC Memo to supplement CMC Review #1
3. MEMO DATE: 08-AUG-2011
4. REVIEWER: Anne Marie Russell, Ph.D.
5. PREVIOUS DOCUMENTS: See CMC Review #1 which covers documents through SDN 27.
6. SUBMISSION(S) BEING REVIEWED: This is an electronic submission. To expedite review, some amendments were submitted via electronic mail prior to submission to the NDA.

Submission type	Content	Date Letter date in EDR	SDN
Amendment	Assessment of launch supply materials (unsolicited).	19-JUL-2011	29
Amendment	Response to teleconference #4 held on 28-JUL: data on validation batches M0020-22	29-JUL-2011	32
Amendment	Corrected tables, additional MBP release and stability data, clarification of attributes	03-AUG-2011	33
Amendment	Post-approval stability protocol for DS and MBP.	04-AUG-2011	34
Amendment	Labeling and Medication Guide	05-AUG-2011	35

7. NAME & ADDRESS OF APPLICANT:

Name:	Hoffman-LaRoche, Inc.
Address:	340 Kingsland St. Nutley, NJ 07110-1199
Representative:	Duane Voss, Program Director, Regulatory Affairs
Telephone:	973-562-3519

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zelboraf
b) Non-Proprietary Name (USAN): vemurafenib/ RO5185426
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem Type: 1 (new molecular entity)
- Submission Priority: expedited priority

9. LEGAL BASIS FOR SUBMISSION:

NDA (b) (4) was submitted in accordance with 21 CFR Part 314.50.

10. PHARMACOL. CATEGORY: kinase inhibitor

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 240 mg

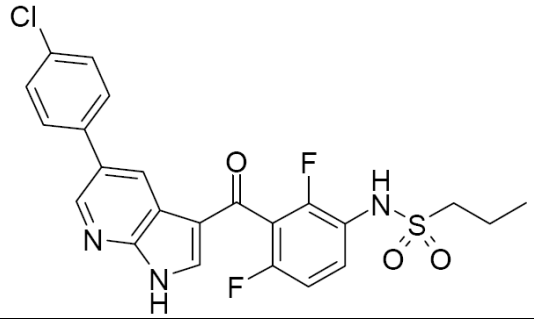
13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s)	
Propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide Roche: RO5185426-000 (b) (4) crystalline API) Plexxikon: PLX4032	
Empirical Formula	$C_{23}H_{18}ClF_2N_3O_3S$
Molecular Weight	489.93 g/mol
CAS Registry Number	918504-65-1
Structural Formula	

17. RELATED/SUPPORTING DOCUMENTS: N/A

B. Other Documents: IND 73,620

18. STATUS:

Only those which are updated from CMC Review #1 (15-JUL-2011) are included in the table.

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	acceptable	19-JUL-2011	
Pharm/Tox	acceptable	27-JUL-2011	David McGuinn

Chemistry Memo

This memo is a follow-on to expedited priority CMC Review #1 (15-JUL-2011). It covers additional CMC material submitted to the active NDA subsequent to the finalizing of CMC Review#1 and Division Director's Memo.

Executive Summary:

New CMC information, submitted 19-JUL-2011, advised that the commercial batches of drug product (b) (4)), understood by the Agency to be used to supply launch materials, were not going to be marketed. Instead, launch materials would be supplied from three validation batches (M0020, M0021 and M0022) manufactured in April 2011. These validation batches had not been submitted to the NDA.

Without further action, these three validation batches would be subject to the 12 month drug product expiry and therefore patient supply for launch and beyond was not assured. Consequently, CMC requested additional information on the launch batches to assess the feasibility of exercising regulatory discretion on their expiry to extend shelf life in the interests of avoiding a drug shortage.

In conclusion, employing similar scientific rationale as was presented in CMC Review #1 for commercial batches (b) (4), sufficient information was provided to support the extension of the shelf life of the validation batches M0020, M0021 and M0022 to 24 months, provided additional stability monitoring is performed.

Place the following language in the action letter:

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.

CMC Review

Introduction:

Unsolicited, new CMC information was submitted 19-JUL-2011 (SDN029) and advised that the commercial batches of drug product [redacted] (b) (4) understood by the Agency as the launch materials planned to supply the US, were not going to be marketed. Instead, launch materials would be supplied from three validation batches (M0020, M0021 and M0022) manufactured in April 2011. These validation batches had not been submitted to the NDA.

Without further action, these three validation batches would be subject to the 12 month drug product expiry and therefore patient supply for launch and beyond was not assured. Consequently, in a teleconference on 28-JUL-2011, CMC requested additional information on the launch batches to assess the feasibility of exercising regulatory discretion to extend their shelf life in the interests of avoiding a drug shortage. The applicant submitted the requested information on 29-JUL-2011 (SDN 032) and additional information on 03-AUG-2011 (SDN033) and 04-AUG-2011 (SDN034).

Review of SDN029, SDN032-34: Validation batches for launch

Table 1. Drug Substance and [redacted] (b) (4) batches used to manufacture Validation Batches M0020, M0021 and M0022:

Table 1 Correlation of drug substance, MBP and drug product batches

Drug Product Batch no.	MBP Batch no.	Drug Substance Batch no.	Place of Manufacture	Date of Manufacture	Batch Size (Tablets)	Use of Batch
M0020	BS10120011 BS10120012 BS10120013 BS10120014 BS10120015 BS10120022	BS10090004 BS10090005	Roche S.p.A., Segrate, Italy	April 2011	[redacted] (b) (4)	Validation batch, commercial supply
M0021	BS10120017 BS10120018 BS10120019 BS10120021 BS10120022	BS10090005	Roche S.p.A., Segrate, Italy	April 2011		Validation batch, commercial supply
M0022	BS10120025 BS10120026 BS10120027 BS10120028 BS10120029	BS10090006	Roche S.p.A., Segrate, Italy	April 2011		Validation batch, commercial supply

Drug Substance: Manufacture, release and stability data on the three commercial drug substance batches (BS10090004-6) used were previously submitted in the original NDA, reviewed and found to be acceptable. Six months of long-term (30°C/75%RH) and accelerated (40°C/75%RH) stability data were provided for the three batches. No trends or changes in the stability attributes

were present in the data. A[(b) (4)] month re-test period was granted for the drug substance in the CMC Division Director memo dated 19-JUL-2011.

[(b) (4)] is the drug product [(b) (4)] New release data for the 15 batches of MBP used to manufacture the validation drug product batches (see Table 1 above) were submitted. All batches meet final specifications. Three months of long-term (25°C/60%RH) and accelerated (30°C/75% and 40°C/75%RH) stability data for three of the 15 MBP batches (BS10120011-13) were submitted. No trends or changes in the stability attributes were present in the data.

Shipping controls [(b) (4)] The applicant confirmed that future MBP batches will be subject to the final shipping protocol and receipt testing program.

Drug Product: New release and initial (t=0) stability data were submitted for the three validation batches of drug product (M0020, M0021 and M0022). All data met specifications.

Shipping controls [(b) (4)] Comparison of the bulk tablet release data and the initial stability data on the packaged tablets show that all specifications are met. This comparison will suffice at this point to demonstrate that the quality of the tablets was not adversely affected by the [(b) (4)] shipping and the absence of receipt testing for these three validation batches, under these circumstances.

Drug Product Stability Commitment: Validation batches M0020, M0021 and M0022.
The applicant submitted a commitment to conduct additional long term testing on the three validation batches, every three months, through to the end of the shelf-life. This commitment is intended to support an extension of the expiry, if granted by exercise of regulatory discretion to provide for patient supply during launch. The following table lists the post-approval stability program specific for the three validation batches. The list of attributes which will be measured on stability for this special stability program are identical to those tested in the post-approval stability program.

2. STABILITY COMMITMENT

Stability studies on the three full scale validation batches packaged in HDPE bottles with desiccant (M0020, M0021 and M0022) will be performed according to the testing schedule described in Table 2.

Table 2 Testing frequency and storage conditions of the stability studies for the three validation batches

Storage conditions	Testing frequency [months]								
	0	3	6	9	12	15	18	21	24
25°C/60% r.h.	x	x	x	x	x	x	x	x	x
30°C/75% r.h.		x	x	x	x	x	x	x	x
40°C/75% r.h.		x	x						

r.h. : relative humidity
x : analyzed

The following items will be tested:

- Description (Color)
- Content per Tablet of RO5185426-000
- Degradation Products
  - Unspecified, each
  - Total of all
- Water Content
- Modification (Physical Form)
  (b) (4) (Crystalline Form II (b) (4))
- Dissolution

Drug Product expiry and extension by regulatory discretion:

The drug substance, MBP and the drug product are all very stable under long term storage conditions, showing no change in attributes in all data submitted. However, the amorphous form of the drug substance, (b) (4) MBP as well as the drug product, is inherently unstable in form (b) (4) Thus much care needs to be exercised in extrapolating stability data for expiry, (b) (4) .

The reviewed data on which the 12 month expiry was granted for the packaged tablets in CMC Review #1 and Division Director's Memo are listed in the following stability data summary table. The limited amount of primary stability data was due to the expedited nature of this priority NDA. While extrapolation of stability by 6 months is in accordance with ICH Q1E when accelerated stability data indicates no trends, as in this case, the 12 month expiry was granted with caution due to the non-linear stability (b) (4) materials. The 18 month and 12 month stability data were carefully evaluated for changes, but none were found – which was significant support for the extrapolation as well.

Drug Product Stability Data Summary				
		Months of stability data submitted to NDA		
Drug Product Batch numbers	scale/site/type of stability data	Long term 25°C/60%RH	Accelerated 30°C/75%RH	Accelerated 40°C/75%RH
PT9681T06	pilot/Basel/secondary	18	18	6
PT2319BA01A		12	12	6
PT2319BA02A		12	12	6
PT9710T03A	pilot/Segrate/secondary	6	6	6
PT9710T04A		6	6	6
PT9710T05		6	6	6
PT9710T06	full scale/Segrate/primary	6	6	6
PT9710T07		6	6	6
PT9710T08		6	6	6

The release and initial (t=0) stability data for the three validation batches, M0020-22, newly submitted in the amendments reviewed in this memo, all meet specifications. The scientific and regulatory justification for extending the expiry of these validation batches to 24 months to address the launch supply concerns, are similar to that described in CMC Review#1 for the commercial batches which were understood at the time to be intended to supply launch materials. Given the stability of the drug product demonstrated in submitted data, and the added assurance of increased, quarterly stability testing, the extension of the shelf life of the three validation batches (M0020, M0021 and M0022) to 24 months for launch materials is acceptable in the interests of avoiding a drug shortage.

Labeling/PI andMedication Guide: Review of version submitted in SDN035 (5-AUG-2011)

Section Number Section Title	Original version, as submitted	CMC recommends:
16 How Supplied Storage and Handling	Store at room temperature 25°C (77°F); excursions permitted between 15°C and 30°C (59° F and 86°F).	Store at room temperature 20°C -25°C (68°F -77°F); excursions permitted between 15°C and 30°C (59° F and 86°F).
16 How Supplied Storage and Handling	none	Store in the original container with the lid tightly closed.
17 Med Guide	***How should I store TRADENAME?*** • Store TRADENAME at room temperature, (b) (4) (b) (4)	***How should I store ZELBORAF?*** Store ZELBORAF at room temperature between 68°F to 77°F (20°C to 25°C).
17 Med Guide	• (b) (4)	Store ZELBORAF in the original container with the lid tightly closed.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ANNE M RUSSELL
08/09/2011

SARAH P MIKSINSKI
08/09/2011
Concur

ONDQA Division Director's Memo
NDA 202429, Zelboraf Tablets, 240 mg
Date: 19-JUL-2011

Introduction

Zelboraf (vemurafenib) Tablets are an immediate-release (IR), film-coated tablet available in one strength; 240 mg. The inactive ingredients in the vemurafenib tablet core are hypromellose acetate succinate, croscarmellose sodium, colloidal silicon dioxide, hydroxypropyl cellulose, and magnesium stearate. The tablet film-coat consists of polyvinyl alcohol, talc, iron oxide red, polyethylene glycol 3350, and titanium dioxide.

The daily recommended dose of vemurafenib is 960 mg (4 tablets) twice daily, with or without food.

All CMC-related deficiencies have been resolved for this application, and all related reviews are complete. There are no outstanding deficiencies that would preclude a recommendation of approval from a CMC standpoint.

ONDQA recommends approval of this NDA. **This recommendation covers all official CMC submissions with receipt dates prior to the date of this memorandum (19-JUL-2011).** ***NOTE: Expiration dating information to be included in action letter is included herein*.**

Administrative

The original submission of this 505(b)(1) NDA was received 27-APR-2011 from Hoffman-La Roche, Inc. Five (5) CMC amendments were also reviewed during the review cycle. All Chemistry, Manufacturing and Controls assessments are captured in the following reviews, respectively: Chemistry Review #1 for both drug substance and drug product (19-JUL-2011) and Biopharmaceutics Review #1 (08-JUL-2011).

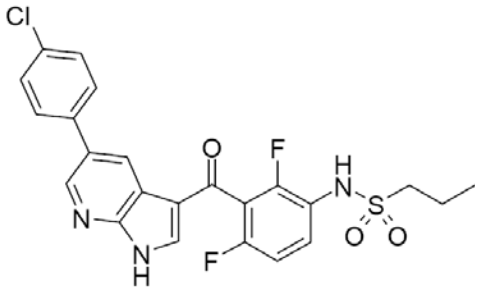
The NDA is supported by IND 73,620 and two (2) drug master files (DMFs). An overall "acceptable" recommendation was issued in EES (19-JUL-2011), and reviews from Clinical Pharmacology (13-JUL-2011), Biopharmaceutics (08-JUL-2011), and DMEPA (see letter dated 08-JUN-2011 and review dated 27-MAY-2011) recommend approval of the application. As of the date of this memorandum, the Pharmacology/Toxicology review is still pending.

Additional container/carton labeling recommendations from DMEPA (27-MAY-2011 review) were identified and are also discussed in the CMC review. The Applicant's proposed trade name (Zelboraf) was found to be acceptable by DMEPA in a letter dated 08-JUN-2011.

This NDA is recommended for approval from a Chemistry, Manufacturing and Controls standpoint. ***NOTE: Expiration dating information to be included in action letter is included herein.***

Drug Substance (Vemurafenib)

Chemical Name: Propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide (MW=489.93 g/mol, $C_{23}H_{18}ClF_2N_3O_3S$)



Vemurafenib is a new molecular entity. [redacted] The compound exists in several polymorphic forms of which the crystalline Form II is the intended form for commercialization. Form II is poorly soluble in water and has low bioavailability (BC Class IV drug). Vemurafenib is relatively stable, and no extraordinary storage precautions are required other than standard protection from oisture and light. The proposed **re-test period period of** [redacted] **months** when stored in the recommended container closure system (protected from light and moisture) at ambient storage conditions is granted.

Drug Product (Vemurafenib Tablets, 240 mg)

The drug product is an IR film-coated tablet and is supplied in one strength; 240 mg. Excipients used in the formulation are conventional and include hypromellose acetate succinate, croscarmellose sodium, colloidal silicon dioxide, hydroxypropyl cellulose, and magnesium stearate. The tablet film-coat consists of polyvinyl alcohol, talc, iron oxide red, polyethylene glycol 3350, and titanium dioxide.

To improve the solubility and bioavailability of the drug, [redacted] formulation was developed to stabilize the amorphous form of vemurafenib. [redacted]

The stability of the [redacted] was assessed in great detail during the CMC review. Specific details are captured in the CMC review, and the stability considerations factored highly into the CMC reviewer's recommendation of expiration dating period for the drug product. During the review, several discussions were conducted with the Applicant regarding the issue of MBP and drug product, with specific focus on the proposed expiration dating period.

Based on the totality of the submitted stability data package, an expiration dating period of [redacted] An expiration dating period of 12 months at the 25°C storage condition is granted for the drug product (tablets).

A final teleconference was conducted between the Agency and the Applicant on 12-JUL-2011 to confirm understanding of issues surrounding the expiration dating period. During this teleconference, the Agency confirmed that regulatory discretion may be exercised by the ONDQA Division Director to extend the shelf life of the three commercial batches of drug product intended to supply launch materials (b) (4) in the interests of avoiding a drug shortage and provided additional stability data is collected and is supportive through the end of the shelf life. The Applicant agreed with this approach; therefore, such discretion is being used to grant a 12-month extension to the previously granted (above) 12-month expiry, resulting in a 24-month expiration dating period only for the three launch batches (b) (4) The Applicant agreed to provide quarterly stability updates for these three launch batches through the end of expiry, in addition to conducting the standard post-approval stability program.

The commercial packaging is 120-count HDPE bottles. (b) (4) Based on the stability data provided and in accordance with ICH Q1E, the Agency grants a 12 month expiry for the 240 mg tablets when packaged in the commercial configuration and when stored at USP controlled room temperature.

Place the following language in the action letter:

(b) (4)

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/s/

RICHARD T LOSTRITTO
07/19/2011

NDA 202-429

Zelboraf (vemurafenib) film-coated tablets

Hoffman-La Roche, Inc.

Anne Marie Russell, Ph.D.
Review Chemist

Office of New Drug Quality Assessment
Division I Branch II
for
The Division of Drug Oncology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 202-429

2. REVIEW #1

3. REVIEW DATE: 15-JUL-2011

4. REVIEWERS: Anne Marie Russell, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED: This is an electronic submission. To expedite review, some amendments were submitted via electronic mail prior to submission to the NDA. Some email clarifications regarding information requests are not listed but are included in amendment cover letters.

Submission type	**Content (See Appendix for IR and teleconference)**	**Date Letter date in EDR**	**SDN**
Original	NDA	27-APR-2011	3
Amendment	Initial response to IR#1	01-JUN-2011	10
Amendment	Second response to IR#1	16-JUN-2011	17
Amendment	Response to IR#2 and teleconference #1 held on 21-JUN	06-JUL-2011 (via email 24-JUN-2011)	24
Amendment	Response to IR#2 issue #4 and teleconference #2 held on 27-JUN	11-JUL-2011 (via email 05-JUL-2011)	25
Amendment	Response to teleconference #3 held on 12-JUL	(via email 13-JUL-2011)	

7. NAME & ADDRESS OF APPLICANT:

Name:	Hoffman-LaRoche, Inc.
Address:	340 Kingsland St. Nutley, NJ 07110-1199
Representative:	Duane Voss, Program Director, Regulatory Affairs
Telephone:	973-562-3519

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zelboraf
b) Non-Proprietary Name (USAN): vemurafenib/ RO5185426
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem Type: 1 (new molecular entity)
- Submission Priority: expedited priority

9. LEGAL BASIS FOR SUBMISSION:

NDA (b) (4) was submitted in accordance with 21 CFR Part 314.50.

10. PHARMACOL. CATEGORY: kinase inhibitor

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 240 mg

13. ROUTE OF ADMINISTRATION: oral

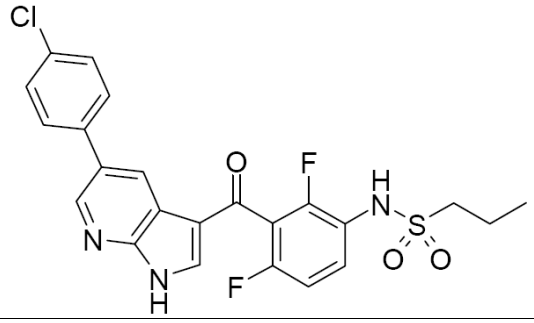
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed

___X___ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s)	
Propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide Roche: RO5185426-000 ((b) (4) crystalline API) Plexxikon: PLX4032	
Empirical Formula	$C_{23}H_{18}ClF_2N_3O_3S$
Molecular Weight	489.93 g/mol
CAS Registry Number	918504-65-1
Structural Formula	

17. RELATED/SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)		4	N/A	15-JUL-2011	Reviewed by Anne Marie Russell, Ph.D.
	III			4	N/A	15-JUL-2011	Reviewed by Anne Marie Russell, Ph.D.

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: IND 73,620

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	pending	15-JUL-2011	See post-review memo in DARRTS
Pharm/Tox	pending	15-JUL-2011	David McGuinn
Biopharm	Recommends approval	08-JUL-2011	Deepika Lakhani, Ph.D.
Labeling Nomenclature Committee (LNC)	N/A	N/A	N/A
Methods Validation	Acceptable	N/A	Methods are standard; no methods require post-approval validation.
DMEPA	Consult-Review - labeling	27-MAY-2011	Lubna
EA	Categorical Exclusion Claim under 21 CFR 25.31(a)- new NDA - Acceptable	15-JUL-2011	Anne Marie Russell, Ph.D.
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 202-429

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

As amended, this New Drug Application for Zelboraf (vemurafenib) Tablets, 240-mg, is recommended for approval from the Chemistry, Manufacturing and Controls perspective, pending an overall recommendation of Acceptable issued by the Office of Compliance.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

(1) Drug Substance

Vemurafenib (RO5185426) is a novel small molecule with the crystalline Form II being the most stable polymorphic form with poor aqueous solubility and low bioavailability (BCS Class IV drug). These properties directly affected drug product formulation development.

Critical quality attributes of the drug substance including identification, assay, and purity. (b) (4)

The drug substance is relatively stable; no extraordinary storage precautions are required other than standard protection from moisture and light. A retest period of (b) (4) months at 25°C storage condition is supported by drug substance stability data.

(2) Drug Product

The drug product is supplied as film-coated tablets containing 240 mg of vemurafenib for oral administration. The tablets are oval, biconvex, pinkish white to orange white film-coated tablets engraved with VEM on one side. Inactive ingredients include: Tablet Core: hypromellose acetate succinate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, and hydroxypropyl cellulose. Coating: pinkish white: poly(vinyl alcohol), titanium dioxide, polyethylene glycol 3350, talc, and iron oxide red.

To improve the apparent solubility and bioavailability of the crystalline Form II, (b) (4) formulation was developed (b) (4) (b) (4)

(b) (4)

Tablets are film-coated, released per specifications, transported in bulk to the final packaging site and packaged into HDPE bottles with an integrated dessicant.

(b) (4)

The stability of MBP and drug product has been demonstrated under ICH conditions. (b) (4) An expiry of 12 months at 25°C storage condition is granted for the drug product (tablets) and is supported by drug product stability data .

Regulatory discretion may be exercised by the ONDQA Division Director to extend the shelf life of the three commercial batches of drug product intended to supply launch materials (b) (4) in the interests of avoiding a drug shortage, provided additional stability data is collected and is supportive through the end of the shelf life. See Division Director memo for details.

B. Description of How the Drug Product is Intended to be Used

The proposed dose of vemurafenib in adult patients is 960 mg (four 240 mg tablets) twice daily. The product is supplied in bottles of 120. The tablets are to be stored in the original HPDE bottle, which includes an integrated dessicant unit. The drug product is to be stored at 25°C (with excursions permitted to 15°-30°C) [USP controlled room temperature]. The approved expiry of 12-months when stored as directed is supported by stability data.

C. Basis for Approvability or Not-Approval Recommendation

The requirements of 21 CFR 314.50(d)(1) have been adequately met by the applicant, pending overall recommendation of Acceptable issued by the Office of Compliance. All drug substance

and drug product manufacturing, packaging and control facilities were submitted to EES. The tablet manufacturing facility (Segrate, Italy) was inspected. At the time of completion of this review, an overall recommendation was pending from the Office of Compliance.

III. Administrative

A. Reviewer's Signature *{see electronic signature page}*

B. Endorsement Block *{see electronic signature page}*

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/s/

ANNE M RUSSELL
07/18/2011

SARAH P MIKSINSKI
07/19/2011

Initial Quality Assessment
Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

OND Division:	**Division of Drug Oncology Products**
NDA:	**202-429 (Seq-001 for CMC)**
Applicant:	**Hoffmann-La Roche Inc.**
Stamp Date:	**28 April, 2011**
PDUFA Goal Date:	**28 October, 2011 (Priority)**
Established Name:	**Vemurafenib**
Trade Name	**Zelboraf (proposed)**
Dosage Form and Strength:	**Tablet – 240 mg**
Route of Administration:	**Oral**
Indication:	**Unresectable Stage lllc or Stage IV BRAF mutation-positive melanoma by the cobas0 4800 BRAF V600 Mutation Test.**
eCTD Reference for CMC	**eCTD.**
Regulatory Filing	**For 505 (b) (1)**
Related IND	**IND 73,620** (b) (4)
Assessed by:	**Haripada Sarker**

	Yes	No
ONDQA Fileability:	x	
Comments for 74-Day Letter:		x

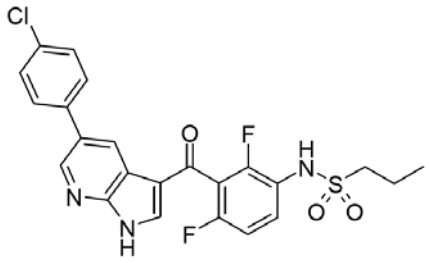
Background Summary

The application introduces the drug, Vemurafenib as a new molecular entity. Vemurafenib is supplied as a tablet containing 240 mg of active ingredient for oral administration. Several DS and DP CMC related issues were discussed in a CMC specific EOP2 meeting dated July 17, 2009 (see meeting minutes in DARRTS). The issues involved starting material, (b) (4), stability data, etc. The NDA is submitted as per eCTD format.

Drug Substance (DS)

(b) (4) The DS is identified and characterized as following.

Chemical Name: propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1Hpyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide: DS is also designated as laboratory code, RO5185426.



No chiral center is associated with the DS molecule. RO5185426 is a white to off white, crystalline, non-hygroscopic powder, exist in several polymorphic forms, which can be distinguished by XRPD. Polymorphic Form II is the most stable polymorphic form and is selected for the commercial production. RO5185426 is a BCS Class IV drug (low permeability - poor solubility).

The DS is manufactured and controlled by:

Hoffmann-La Roche Ltd.
Grenzacherstrasse 124
CH-4070 Basel, Switzerland

DS manufacturing process controls (b) (4) are elaborated with justifications. Five impurities are specified at levels exceeding this applicable qualification threshold because they have been detected in DS batches in amounts that exceeded the qualification threshold. Data from appropriate toxicology studies are provided to qualify the proposed limits. Thirty four development or pilot scale batches and eight commercial scale batches have been reported. Specifications and analytical methods have been established to adequately control the identity, quality, purity and stability of the drug substance. The DS is packaged (b) (4).

Stability data from long-term, stress, and accelerated studies are provided for DS. Samples of six development (pilot-scale) batches and 3 commercial scale batches were stored (b) (4) at 30°C/75% relative humidity (r.h.) for up to 24 months and at 40°C/75% r.h. for up to 6 months. No significant degradation products were found. Process related impurities remained unchanged.

Based on the currently available stability data, a retest period of (b) (4) months is proposed to DS, when packed and stored (b) (4) at controlled room temperature.

DS Critical Issues

- Based on the EOP2 meeting minutes and the information provided in this NDA, the issue of starting material needs to be resolved. Verify the controls and the sources for starting material.

- Verify the controls strategy for 5 DS impurities that are at levels exceeding this applicable qualification threshold.
- Verify the DS proposed retest period of (b) (4) months.

Drug Product (DP)

In this NDA, applicant proposes 240 mg tablet for commercialization. Because of the poor aqueous solubility of DS, the crystalline Form II exhibits low bioavailability. Roche investigated methods to prepare a stabilized non-crystalline formulation. (b) (4)

The following codes are used in this NDA to identify the crystalline API and the drug product (b) (4)

RO5185426-000 Crystalline API (Forms I and II)

(b) (4)

RO5185426-006 (b) (4)

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?		√	Shorter Shelf-life likely.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		CMC issues in pre-NDA meeting appeared to be addressed in the NDA.
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?		√	Tablet formulation.
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM) HPLC assay on DP stability reported statistical analysis (ref. vol 1, p161).	√ √ √ √ **√**		Microbiology Pharm/Tox Biopharm Statistics (stability) OCP/CDRH/CBER LNC DMETS/DMEPA/ODS **EER**

Have all DMF References been identified? Yes (√) No ( )

DMF/IND Number	Holder	Description	LOA Included
[redacted] (b) (4)			Yes
			Yes

Comments and Recommendations
The application is fileable and no 74-Day Letter issue has been identified at this point. However, separate CMC information requested are initiated to expedite the review. Facilities have been entered into EES for inspection. A team approach, including more than one CMC reviewer, is recommended for this NDA, since this application is considered as an expedited priority based on medical need.

Haripada Sarker
CMC Lead

June 6, 2011
Date

Janice Brown, CMC Lead for
Sarah Pope Miksinski, Ph.D.
Branch Chief

June 6, 2011
Date

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

/s/

HARIPADA SARKER
06/07/2011

JANICE T BROWN
06/09/2011
Janice Brown for Sarah Pope Miksinski, Ph.D.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 202429/000	**Action Goal:**	
St. Date:	28-APR-2011	**District Goal:**	29-AUG-2011
Regulatory:	28-OCT-2011		
Applicant:	HOFFMANN LA ROCHE	**Brand Name:**	VEMURAFENIB
	340 KINGSLAND ST	**Estab. Name:**	
	NUTLEY, NJ 07110	**Generic Name:**	
Priority:	1	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	150	001; TABLET; VEMURAFENIB; 240MG	

Application Comment: FROM THE APPLICANT: "TO OVERCOME THE LOW SOLUBILITY AND POOR BIOAVAILABILITY OF CRYSTALLINE RO5185426-000 FORM II, ROCHE DEVELOPED (b) (4) THIS MAY BE A HIGH RISK API PROCEDURE OR A COMPLEX MANUFACTURING PROCESS. TBD (on 28-APR-2011 by S. GOLDIE () 301-796-2055)

THIS APPLICATION WILL LIKELY BE A PRIORITY REVIEW AND MAY BE AN ACCELERATED (EXCEPTED) REVIEW CLOCK. M. STOCK HAS BEEN WORKING ON THIS APPLICATION AS OF 14 APRIL 2011. (on 28-APR-2011 by S. GOLDIE () 301-796-2055)

FDA Contacts:				
	S. GOLDIE	Project Manager		301-796-2055
	A. RUSSELL	Review Chemist	(HFD-530)	301-796-2014
	H. SARKER	Team Leader	(HFD-150)	301-796-1747

Overall Recommendation:	ACCEPTABLE	on 19-JUL-2011	by M. STOCK	(HFD-320)	301-796-4753

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9692013 **FEI:** 3002807200

HOFFMAN LA ROCHE, LTD.

GRENZACHERSTRASSE 124
BASEL, , SWITZERLAND

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE (b) (4)

DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STABILITY TESTER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Estab. Comment: MANUFACTURING, TESTING AND RELEASING (SIC) OF DRUG SUBSTANCE; MANUFACTURING, TESTING OF (b) (4) ; STABILITY TESTING OF DRUG SUBSTANCE, (b) (4) CLINICAL MANUFACTURE, RELEASE AND STABILITY TESTING OF DRUG PRODUCT (TABLETS) (on 28-APR-2011 by S. GOLDIE () 301-796-2055)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

CONTROL TESTING LABORATORY NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	28-APR-2011				GOLDIES
SUBMITTED TO DO	06-MAY-2011	10-Day Letter			STOCKM
D COMMENDATION	19-MAY-2011			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	20-MAY-2011			ACCEPTABLE	SMITHDE
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	28-APR-2011				GOLDIES
OC RECOMMENDATION	29-APR-2011			ACCEPTABLE	STOCKM
				BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE (b) (4)

Estab. Comment: ALTERNATE (b) (4) SITE FOR (b) (4) (on 28-APR-2011 by S. GOLDIE () 301-796-2055)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	28-APR-2011				GOLDIES
OC RECOMMENDATION	29-APR-2011			ACCEPTABLE	STOCKM
				BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9616956 **FEI:** 3000298591

PRODUCTOS ROCHE SA

SEVERO OCHOA 13
LEGANES, MADRID, SPAIN 28914

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Estab. Comment:

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	28-APR-2011				GOLDIES
OC RECOMMENDATION	29-APR-2011			ACCEPTABLE	STOCKM
				BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:** 3003716872

ROCHE S.P.A.

VIA MORELLI 2
SEGRATE, , ITALY

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

Estab. Comment: TABLET MANUFACTURE AND TESTING (on 28-APR-2011 by S. GOLDIE () 301-796-2055)

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	28-APR-2011				GOLDIES
SUBMITTED TO DO	29-APR-2011	Product Specific			PHILPYE
ASSIGNED INSPECTION TO IB HIGH PRIORITY!	29-APR-2011	Product Specific			PHILPYE
INSPECTION SCHEDULED	16-MAY-2011		24-JUN-2011		IRIVERA
DO RECOMMENDATION	19-JUL-2011			ACCEPTABLE INSPECTION	PHILPYE
OC RECOMMENDATION	19-JUL-2011			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM