CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203388Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

To: NDA 203388

From: Sarah Pope Miksinski, Ph.D.

Date: 1/30/2012

Re: Final CMC recommendation for NDA 203388

NDA 203388 (Erivedge®) was initially submitted on 08-SEP-2011 and was granted an expedited priority review by the Agency. Chemistry Reviews for drug substance and drug product (both dated 20-JAN-2012), as well as the ONDQA Division Director's Memorandum dated 23-JAN-2012 recommend approval of the NDA from a CMC perspective, provided that an overall acceptable recommendation was later issued from the Office of Compliance. As of the date of the three ONDQA primary and secondary reviews, this recommendation had not been finalized by the Office of Compliance.

This memo serves to update that status. The Office of Compliance issued an overall acceptable recommendation for this application on 24-JAN-2012. This resolves the only remaining issue in the previous CMC reviews.

All CMC deficiencies have been resolved, there is now a final acceptable recommendation from the Office of Compliance, and there are no other outstanding CMC issues with this NDA. Therefore, approval of NDA 203388 is recommended from a CMC perspective.

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/s/

SARAH P MIKSINSKI
01/30/2012

ONDQA Division Director's Memo
NDA 203-388, Erivedge Capsules, 150 mg
Date: 20-JAN-2012

Introduction

Erivedge (vismodegib) Capsules are an immediate release hard gelatin capsule formulation to be marketed in one strength – 150 mg. The inactive ingredients, including the components used in the capsule shell and printing ink, are compendial grade and standard for oral capsule formulations.

The recommended dose of ERIVEDGE is 150 mg taken orally once daily until disease progression or until unacceptable toxicity occurs.

All CMC-related deficiencies have been resolved for this application, and all related reviews are complete. There are no outstanding review deficiencies that would preclude a recommendation of approval from a CMC standpoint. However, as of the date of this memorandum, an overall recommendation from the Office of Compliance has not been received.

All CMC review issues have been resolved, and ONDQA recommends approval of this NDA pending the receipt of an overall "acceptable" recommendation from CDER's Office of Compliance.

Administrative

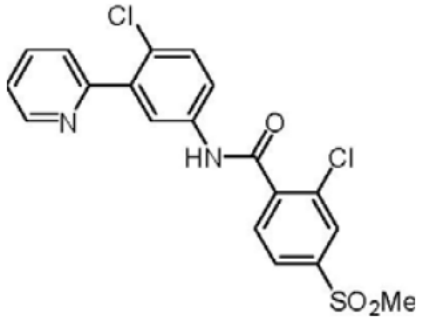
The original submission of this 505(b)(1) NDA was received 08-SEP-2011 from Genentech, Inc. Four (4) solicited CMC amendments were also reviewed during the review cycle. The comprehensive CMC assessment is captured in the following reviews, respectively: Chemistry Review #1 for drug substance (20-JAN-2012, Dr. A. Russell) and Chemistry Review #1 for drug product and Biopharmaceutics (20-JAN-2012, Dr. Z. Dong).

The NDA is supported by IND 74573 and eight (8) drug master files (DMFs). All DMFs were assessed for adequacy in the respective chemistry reviews.

This NDA is recommended for approval from a Chemistry, Manufacturing and Controls standpoint pending the receipt of an overall "acceptable" recommendation from CDER's Office of Compliance.

Drug Substance (Vismodegib)

Chemical Name: 2-Chloro-N-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (MW=421.30 g/mol, $C_{19}H_{14}Cl_2N_2O_3S$)



Vismodegib is a new molecular entity. It contains [redacted] and is the intended [redacted] for commercialization. Vismodegib is practically insoluble in [redacted] at pH 7 and under room temperature (~ 0.1 µg/mL). Vismodegib is [redacted] It is classified as a BCS Class 2 compound due to its low solubility and high permeability.

Vismogenib is stable; no extraordinary storage precautions are required other than standard protection from [redacted] The proposed **re-test period period of [redacted] months** when stored in the recommended container closure system [redacted] at ambient storage (LT 30°C) conditions is granted.

Drug Product (Vismodegib Capsules, 150 mg)

The drug product is an immediate release hard gelatin capsule to be marketed in one strength – 150 mg Excipients used in the formulation are conventional for oral capsules and include microcrystalline cellulose, lactose monohydrate, sodium lauryl sulfate, povidone, sodium starch glycolate, talc, and magnesium stearate. Components of the capsule shell are standard and include red iron oxide, black iron oxide, titanium dioxide, gelatin, and printing ink.

The drug product is manufactured via [redacted] The control strategy for vismodegib drug product includes dispensing controls, controls on critical process parameters/in-process controls and final product testing. A copy of the representative master batch record for commercial manufacturing is provided in the submission.

The commercial packaging configuration is 28-count, 50-mL HDPE bottle. The Applicant proposes a [redacted] month expiry for this product when stored in the commercial packaging at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Based on the stability data provided and in accordance with ICH Q1E, the Agency grants a 24 month expiry for the 150 mg tablets when packaged in the commercial configuration and when stored at USP controlled room temperature.

Place the following language in the action letter:
Based on the provided stability data, an expiration dating period of 24 months is

granted for the drug product when stored at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Thank you,

Richard (Rik) Lostritto, Director, Division-I, ONDQA

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/s/

RICHARD T LOSTRITTO
01/23/2012

NDA 203-388

Erivedge™ (vismodegib) capsules (150 mg)

Genentech, Inc.

CMC Review of Drug Substance
by
Anne Marie Russell, Ph.D., Review Chemist
Office of New Drug Quality Assessment
Division I Branch II

for

Division of Oncology Products 2 (DOP2)

Table of Contents

Chemistry Review Data Sheet

1. NDA 203-388

2. REVIEW #1

3. REVIEW DATE: 17-JAN-2012

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

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 74573 submission	09/29/2006
Original IND 74573 CMC review by Eldon E. Leutzinger	11/20/2006
IND 74573 CMC only Type C meeting minutes	09/25/2009
IND 74573 CMC review on treatment protocol by Haripada Sarker	11/12/2010
(b) (4) CMC only pre-NDA meeting minutes	06/01/2011

6. SUBMISSION(S) BEING REVIEWED (CMC): This is an electronic submission. To expedite review, some amendments were submitted via electronic mail prior to submission to the NDA

Submission(s) Reviewed	Document Date
Original Submission 0000	09/08/2011
Amendment 0023 (Response to CMC IR)	12/28/2011
Amendment 0026 (Response to CMC IR)	01/10/2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Genentech, Inc.
Address:	1 DNA Way, MS#241B South San Francisco, CA 94080-4990
Representative:	Michelle H. Rohrer
Telephone:	(650) 225-1558

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Erivedge™
b) Non-Proprietary Name (USAN): Vismodegib
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: 505(b)(1)

10. PHARMACOL. CATEGORY: inhibitor of the Hedgehog pathway

11. DOSAGE FORM: capsule

12. STRENGTH/POTENCY: 150 mg

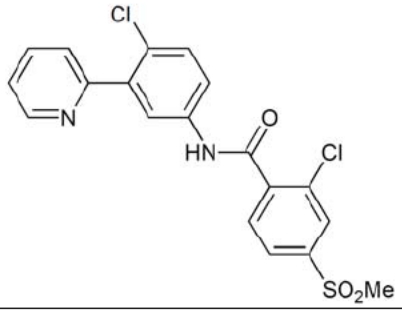
13. ROUTE OF ADMINISTRATION: oral

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)	2-Chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide
Empirical Formula	$C_{19}H_{14}Cl_2N_2O_3S$
Molecular Weight	421.30 g/mol
Structural Formula	

17. RELATED/SUPPORTING DOCUMENTS:
A. **DMFs**: None for Drug Substance
B. Other Documents: IND 74,573

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	See Drug Product review	01/13/2012	Youngsook Jeon
EES	Pending		Mahesh Ramanadham
Pharm/Tox	See Pharm Tox review	01/13/2012	Denali Kufrin
Biopharm	Approval	01/20/2012	Zedong Dong
LNC	N/A		
Methods Validation	See Drug Product review	01/20/2012	Zedong Dong
DMEPA	N/A		
EA	Category exclusion	09/28/2011	Raanan A. Bloom
Microbiology	Approval	12/21/2011	John Metcalfe

The Chemistry Review for NDA 203-388

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 203-388 is recommended for approval from a Chemistry, Manufacturing and Controls standpoint, pending satisfactory resolution of the Labeling and EES issues.

Refer to the Drug Product Review by Dr. Z. Dong, for language to be inserted into the action letter.

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

Drug Product: ***(reproduced from Dr. Zedong Dong's review of the Drug Product)***

The commercial vismodegib drug product (150 mg) is a hard gelatin capsule formulation manufactured (b) (4) The excipients (including the components in gelatin capsule shell and printing ink) used for manufacturing the drug product are all compendial grade. Vismodegib capsules 150 mg will be provided as pink opaque body/grey opaque cap with "150 mg" printed on the body and "VISMO" printed on the cap with both in black ink. The drug product will be packaged in 50 mL square white HDPE bottles with child-resistant caps (b) (4) (28 counts/bottle).

(b) (4)

The vismodegib drug product is manufactured via standard unit operations (b) (4) The control strategy for vismodegib drug product includes dispensing controls, controls on critical process parameters/in-process controls

(b) (4) and final product testing. A copy of the representative master batch record for commercial manufacturing is provided in the submission.

The specifications of the vismodegib drug product include testing for (b) (4) The non-compendial analytical methods were properly validated. Satisfactory batch analysis results were provided for three primary stability batches (batch# 800526, 800527, and 800528).

Eighteen-month stability results for the primary stability batches were submitted for the long term conditions (30°C/65% RH) and six months under accelerated conditions (40°C/75% RH), for the proposed commercial packaging configuration. No significant trend of change was observed for appearance, assay, degradation, or dissolution during storage. (b) (4) (b) (4) was observed under both storage conditions from (b) (4) Statistical analysis on assay results was submitted from the applicant, but no statistical analysis was performed on dissolution or (b) (4)

Based on the stability results, the recommended expiry for the vismodegib drug product is twenty four months when stored at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Per the applicant, the stability studies for the first three commercial batches of drug product are ongoing. In addition, an annual commercial batch will be placed on stability according to the submitted post-approval stability protocol, provided production warrants.

Immediate container and carton labeling was submitted for the proposed commercial packaging configuration, which appears acceptable.

Per the review by Raanan A. Bloom, claim for category exclusion is granted per 21 CFR Part 25.31 (b).

Drug Substance:

The vismodegib drug substance is a novel small molecule (b) (4) Critical quality attributes of the drug substance include (b) (4)

The drug substance is stable; no extraordinary storage precautions are required other than (b) (4). A retest period of (b) (4) months at (b) (4) storage condition is supported by drug substance stability data.

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

The proposed dose of vemurafenib in adult patients is 150 mg (1 capsule) daily. Vismodegib capsules are available in 150 mg strength in 28 counts/bottle packaging configuration. The

capsules are recommended to be stored at 20°C to 25°C (68°F to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F). A twenty-four month expiry at the proposed storage conditions will be granted based on the provided stability data. This is to be communicated to the applicant in the action letter.

C. Basis for Approvability or Not-Approval Recommendation *(harmonized with the Drug Product Review)***:**
This new drug application (203-388) is recommended to be approved from the CMC perspective pending an overall recommendation of the cGMP status of the manufacturing and testing facilities from the Office of Compliance. The recommendation for approval is based upon the acceptable identity, strength, quality, and purity upon the evaluation of the drug substance and drug product.
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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
01/20/2012

SARAH P MIKSINSKI
01/20/2012

NDA 203-388

Erivedge™ (vismodegib) Capsules

(150 mg)

Genentech, Inc.

Zedong Dong, Ph.D.

Product Quality Reviewer
CMC-DRUG PRODUCT AND BIOPHARMACEUTICS

Office of New Drug Quality Assessment, Division I

CMC AND BIOPHARMACEUTICS REVIEW OF NDA 203-388
DRUG PRODUCT

For the Division of Oncology Products 2 (HFD-150)

Table of Contents

Product Quality Review Data Sheet

1. NDA 203-388

2. REVIEW #: 1

3. REVIEW DATE: January 13, 2012

4. REVIEWER: Zedong Dong, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 74573 submission	09/29/2006
Original IND 74573 CMC review by Eldon E. Leutzinger	11/20/2006
IND 74573 CMC only Type C meeting minutes	09/25/2009
IND 74573 CMC review on treatment protocol by Haripada Sarker	11/12/2010
IND 74543 CMC only pre-NDA meeting minutes	06/01/2011

6. SUBMISSION(S) BEING REVIEWED (CMC):

Submission(s) Reviewed	Document Date
Original Submission 0000	09/08/2011
Amendment 0009 (Response to CMC IR)	10/17/2011
Amendment 0015 (Response to CMC IR)	11/23/2011
Amendment 0017 (Technical amendment)	11/29/2011
Amendment 0021 (Labeling)	12/21/2011
Amendment 0022 (Labeling)	12/22/2011
Amendment 0023 (Response to CMC IR)	12/28/2011
Amendment 0024 (LOA to DMF (b) (4)	01/03/2012
Amendment 0026 (Response to CMC IR)	01/10/2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Genentech, Inc.
Address:	1 DNA Way, MS#241B South San Francisco, CA 94080-4990

Representative: Michelle H. Rohrer

Telephone: (650) 225-1558

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Erivedge™
b) Non-Proprietary Name (USAN): Vismodegib
c) Code Name/# (ONDC only): GDC-0449
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Advanced basal cell carcinoma

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 150 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

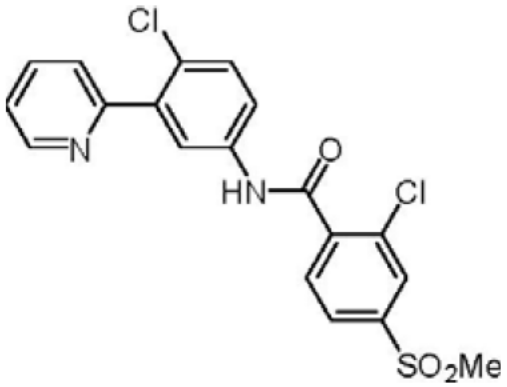
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names:

2-Chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide

Molecular Formula: $C_{19}H_{14}Cl_2N_2O_3S$

Molecular Weight: 421.30 g/mol



Vismodegib

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4) (b) (4)	1	Adequate	01/13/2012	
	IV		(b) (4)	3	Adequate	06/23/2010	By Dr. Stuart Zimmerman
	III		(b) (4)	4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A
	III			4	N/A	N/A	N/A

[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 adequate data in the application, therefore the DMF was not reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	See body of text	01/18/2012	Youngsook Jeon
EES	Pending		Mahesh Ramanadham
Pharm/Tox	N/A		
Biopharm	Approval	01/20/2012	Zedong Dong
LNC	N/A		
Methods Validation	Requested for (b) (4) (b) (4)		
DMEPA	N/A		
EA	Category exclusion	09/28/2011	Raanan A. Bloom
Microbiology	Approval	12/21/2011	John Metcalfe

Executive Summary Section

The CMC and Biopharmaceutics Review for NDA 203-388

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 203-388 is recommended for approval from a Chemistry, Manufacturing and Controls (CMC) and Biopharmaceutics standpoint, pending satisfactory resolution of the Labeling and EES issues.

Insert the following language into the action letter:
Based on the provided stability data, an expiration dating period of 24 months is granted for the drug product when stored at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

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

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

The commercial vismodegib drug product (150 mg) is a hard gelatin capsule formulation manufactured (b) (4) The excipients (including the components in gelatin capsule shell and printing ink) used for manufacturing the drug product are all compendial grade. Vismodegib capsules 150 mg will be provided as pink opaque body/grey opaque cap with "150 mg" printed on the body and "VISMO" printed on the cap with both in black ink. The drug product will be packaged in 50 mL square white HDPE bottles with child-resistant caps (b) (4) (28 counts/bottle).

(b) (4)

(b) (4)

Executive Summary Section

(b) (4)

The vismodegib drug product is manufactured via standard unit operations, (b) (4) The control strategy for vismodegib drug product includes dispensing controls, controls on critical process parameters/in-process controls (b) (4) and final product testing. A copy of the representative master batch record for commercial manufacturing is provided in the submission.

The specifications of the vismodegib drug product include (b) (4) The non-compendial analytical methods were properly validated. Satisfactory batch analysis results were provided for three primary stability batches (batch# 800526, 800527, and 800528).

Eighteen-month stability results for the primary stability batches were submitted for the long term conditions (30°C/65% RH) and six months under accelerated conditions (40°C/75% RH), for the proposed commercial packaging configuration. No significant trend of change was observed for appearance, assay, degradation, or dissolution during storage. (b) (4) Statistical analysis on assay results was submitted from the applicant, but no statistical analysis was performed on dissolution or water content.

Based on the stability results, the recommended expiry for the vismodegib drug product is twenty four months when stored at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Per the applicant, the stability studies for the first three commercial batches of drug product are ongoing. In addition, an annual commercial batch will be placed on stability according to the submitted post-approval stability protocol, provided production warrants.

Executive Summary Section

Immediate container and carton labeling was submitted for the proposed commercial packaging configuration, which appears acceptable.

Per the review by Raanan A. Bloom, claim for category exclusion is granted per 21 CFR Part 25.31 (b).

Drug Substance:
(reproduced from Dr. Anne Marie Russell's Review)

The vismodegib drug substance is a novel small molecule [redacted] (b) (4)

The drug substance is stable; no extraordinary storage precautions are required other than standard protection from moisture and light. A retest period of [redacted] (b) (4) months at no greater than 30°C storage condition is supported by drug substance stability data.

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

Vismodegib capsules are available in 150 mg strength in 28 counts/bottle packaging configuration. The capsules are recommended to be stored at 20°C to 25°C (68°F to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F). A twenty-four month expiry at the proposed storage conditions will be granted based on the provided stability data. This is to be communicated to the applicant in the action letter.

C. Basis for Approvability or Not-Approval Recommendation *(Harmonized with DS review)*

This new drug application (203-388) is recommended to be approved from the CMC perspective pending an overall recommendation of the cGMP status of the manufacturing and testing facilities from the Office of Compliance. The recommendation for approval is based upon the acceptable identity, strength, quality, and purity upon the evaluation of the drug substance and drug product.

III. Summary of Biopharmaceutics Assessments

The proposed dissolution method for vismodegib capsules (150 mg) use [redacted] (b) (4) (b) (4) The proposed dissolution specification is Q = [redacted] (b) (4) (b) (4) which is supported by the dissolution results of the drug product lots used in pivotal clinical trial, and drug product lots for primary stability purpose. Upon evaluation, the proposed dissolution method and dissolution

acceptance criterion (Q = (b) (4) (b) (4) for vismodegib capsules (150 mg) are deemed acceptable to support the approval of the NDA.

IV. Administrative

A. Reviewer's Signature

(*see appended electronic signature page*)

Zedong Dong, Ph.D.
CMC and Biopharmaceutics Reviewer
Division I, ONDQA

B. Endorsement Block

(*see appended electronic signature page*)

Angelica Dorantes, Ph.D.
Supervisory Lead (Acting)
ONDQA, Biopharmaceutics

Sarah Pope Miksinski, Ph.D.
Branch Chief
Brach II, Division I, ONDQA

C. CC Block: entered electronically in DARRTS

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/s/

ZEDONG DONG
01/20/2012

ANGELICA DORANTES
01/20/2012

SARAH P MIKSINSKI
01/20/2012

Initial Quality Assessment
Branch II
Pre-Marketing Assessment Division I
Office of New Drug Quality Assessment

OND Division:	Division of Oncology Drug Products 2
NDA:	20-3388 (e-submission)
Applicant:	Genentech, Inc.
Stamp Date:	8 September , 2011
PDUFA Goal Date:	8 September, 2011 (Priority)
Established Name:	Vismodegib
Trade Name	Erivedge
Dosage Form and Strength:	Capsules; 150 mg
Route of Administration:	Oral
Indication:	for use in the treatment of patients with advanced basal cell carcinoma for whom surgery is inappropriate.
eCTD Reference for CMC	NDA 203388 (Module 2 and 3)
Regulatory Filing	For 505 (b) (1)
Related IND	IND 074573 and IND103846
Assessed by:	Liang Zhou

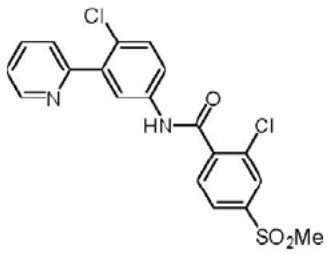
	Yes	No
ONDQA Fileability:	x	
Comments for 74-Day Letter:	x**Background Summary**	

Vismodegib is indicated for the treatment of patients with advanced (metastatic or unresectable, locally advanced) basal-cell carcinoma. The proposed commercial formulation for vismodegib is an immediate-release 150 mg capsule manufactured using a [redacted] (b) (4) The proposed dosing regimen of vismodegib is 150 mg given orally daily.

Drug Substance (DS)

Vismodegib (CAS-Registry Number 879085-55-9), also known as GDC-0449, is a small-molecule inhibitor of the hedgehog (Hh) signal pathway with a molecular weight of 421.30 g/mol. The International Union of Pure and Applied Chemistry name for vismodegib is:
2-chloro-*N*-(4-chloro-3-pyridin-2-yl-phenyl)-4-methanesulfonyl-benzamide

The structure of the molecule is shown in Figure 1.



Vismodegib is an [redacted] white–to–tan crystalline powder with a molecular weight of 421.30 g/mol. It is a free base and has one pKa (3.8) as determined by potentiometric titration. Vismodegib exhibits pH-dependent solubility and is [redacted]. Vismodegib has been classified as a Class 2 molecule under the Biopharmaceutics Classification System (BCS).

The vismodegib manufacturing process involves [redacted]

DS Critical Issues:
EER is submitted into EES system.
Acceptance criteria of impurities and residual solvents need to be further evaluated.

Drug Product (DP)

The proposed commercial formulation for vismodegib is an immediate-release 150 mg capsule manufactured using a [redacted] The proposed dosing regimen is 150 mg given orallydaily.

[redacted]

18 months primary stability data at 30°C/65% RH (long-term storage condition) and 6 months of stability data at 40°C/75% RH are provided. Based on the primary stability data, a shelf life of [redacted] months is proposed.

Drug Product Critical Issues

- EER is submitted into EES system. Check EES of DP site for accuracy.
- Check any substantial differences in manufacturing and stability profile during the clinical studies and proposed commercial site.
- New degradants in DP (finished dosage form), when compared with DS specification This analytical method evaluation should be assessed to determine appropriateness of qualification of the detection level of impurities .
- Need a justification of proposed (b) (4) expiration dating period based on (b) (4) stability data.
- The DP labeling, which is submitted in PLR format, need to be evaluated for its relevant CMC sections.

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?	√		(b) (4) proposed
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
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?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	√ √ √		Microbiology Pharm/Tox pending Statistics (stability) pending LNC DMETS/DMEP A/ODS

		√		EER

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

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

Comments and Recommendations

The application is fileable and no 74-Day Letter issue has been identified at this point. Facilities have been entered into EES for inspection. However, due to the compressed priority review clock, this review could be effectively handled as a team approach (two reviewers, one each for DS and DP section). However, the following IR needs to be conveyed to the applicant:

Provide dissolution profiles and actual individual test results (n=12, mean, minimum and maximum, RSD) for your pivotal Phase 2 and primary stability lots of drug product.

Liang Zhou
CMC Lead

September 30, 2011
Date

Sarah Pope Miksinski, Ph.D.
Branch Chief

September 30, 2011
Date

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/s/

LIANG ZHOU
10/07/2011

SARAH P MIKSINSKI
10/07/2011

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 203388/000	**Action Goal:**	
S Date:	08-SEP-2011	**District Goal:**	08-JAN-2012
Regulatory:	08-MAR-2012		
Applicant:	GENENTECH	**Brand Name:**	ERIVEDGE
	1 DNA WAY MS 241B	**Estab. Name:**	
	SOUTH SAN FRANCISCO, CA 940804990	**Generic Name:**	Vismodegib
Priority:	1	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	107	001; CAPSULE, HARD GELATIN; VISMODEGIB; 150MG	

Application Comment: NME NEW NDA; FOR SCHEDULING CONTACT (DIFFERENT FROM ONSITE CONTACT PROVIDED) CONTACT GREGORY GALLEGOS; TEL: 651-467-2364; TAX: 651-467-3198; EMAIL: GALLEGOS.GREGORY@GENE.COM (on 14-SEP-2011 by T. LAMBERT () 301-796-4246)

FDA Contacts:	D. MESMER	Project Manager	(HFD-800)	301-796-4023
	Z. DONG	Review Chemist		301-796-3885
	L. ZHOU	Team Leader		301-796-1781

Overall Recommendation:	ACCEPTABLE	on 24-JAN-2012	by M. RAMANADHAM	()
	PENDING	on 20-SEP-2011	by EES_PROD	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: DRUG SUBSTANCE PARTICLE SIZE TESTING BY LIGHT SCATTERING FOR LOT RELEASE (on 14-SEP-2011 by T. LAMBERT () 301-796-4246)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	20-SEP-2011				LAMBERTTU
SUBMITTED TO DO	20-SEP-2011	Product Specific			INYARDA
ASSIGNED INSPECTION TO IB	21-SEP-2011	Product Specific			PHILPYE
INSPECTION PERFORMED	(b) (4)		(b) (4)		ROBERT.STEYERT
Please refer to TURBO EIR					
DO RECOMMENDATION	24-JAN-2012			ACCEPTABLE	GODWINF
REVIEW OF EIR, ETC, TL CLEARED, CMS PENDING				INSPECTION	
OC RECOMMENDATION	24-JAN-2012			ACCEPTABLE	RAMANADHAMM
REVIEW OF EIR, ETC, TL CLEARED, CMS PENDING				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: DRUG SUBSTANCE PARTICLE SIZE TESTIGN BY LIGHT SCATTERING FOR LOT RELEASE (on 12-SEP-2011 by T. LAMBERT () 301-796-4246)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	20-SEP-2011				LAMBERTTU
SUBMITTED TO DO	20-SEP-2011	Product Specific			INYARDA
NEW MOLECULAR ENTITY					
DO RECOMMENDATION	21-SEP-2011			ACCEPTABLE	VMATUSOV
PREVIOUS GMP EI DATED (b) (4) IS CLASSIFIED VAI. THERE ARE NO PENDING ENFORCEMENT ACTIONS THAT WOULD IMPACT THIS RECOMMENDATION.				BASED ON FILE REVIEW	
OC RECOMMENDATION	21-SEP-2011			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9616748 **FEI:** 3002861690

PATHEON INC. - BURLINGTON CENTURY OPERATIONS

977 CENTURY DRIVE
BURLINGTON, ONTARIO, CANADA

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Establishment Comment: DRUG PRODUCT LOT RELEASE AND STABILITY TESTING (on 12-SEP-2011 by T. LAMBERT () 301-796-4246)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	20-SEP-2011				LAMBERTTU
OC RECOMMENDATION	20-SEP-2011			ACCEPTABLE	INYARDA
				BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9690045 **FEI:** 3000264888

PATHEON INC. - TORONTO REGION OPERATIONS

2100 SYNTEX COURT
MISSISSAUGA, ONTARIO, CANADA

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment Comment: DRUG PRODUCT MANUFACTURING, PACKAGING (PRIMARY AND SECONDARY), LABELING, ALTERNATE LOT RELEASE, AND STABILITY TESTING (on 12-SEP-2011 by T. LAMBERT () 301-796-4246)

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

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	20-SEP-2011				LAMBERTTU
SUBMITTED TO DO	20-SEP-2011	Product Specific			INYARDA
NEW MOLECULAR ENTITY					
DO RECOMMENDATION	03-OCT-2011			ACCEPTABLE	MROSE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	04-OCT-2011			ACCEPTABLE	SMITHDE
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: DRUG SUBSTANCE STABILITY TESTING AND ALTERNATE LOT RELEASE TESTING FACILITY; DRUG PRODUCT ALTERNATE STABILITY TESTING FACILITY (on 12-SEP-2011 by T. LAMBERT () 301-796-4246)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	20-SEP-2011				LAMBERTTU
SUBMITTED TO DO	20-SEP-2011	Product Specific			INYARDA
NEW MOLECULAR ENTITY					
ASSIGNED INSPECTION TO IB	14-OCT-2011	Product Specific			MFADDEN
INSPECTION PERFORMED	(b) (4)		(b) (4)		MFADDEN
CGMP INSPECTION CONDUCTED FOCUSING ON THE LABORATORY AND QUALITY SYSTEMS. NO FDA 483 ISSUED. SEVERAL VERBAL OBSERVATIONS DISCUSSED AND CORRECTED PRIOR TO THE CLOSE OUT. METHOD VALIDATION AND METHOD TRANSFER COMPLETED. RECOMMEND FIRM AS ACCEPTABLE.					
INSPECTION SCHEDULED	(b) (4)		(b) (4)		MFADDEN
DO RECOMMENDATION	14-NOV-2011			ACCEPTABLE	MFADDEN
CGMP INSPECTION CONDUCTED FOCUSING ON THE LABORATORY AND QUALITY SYSTEMS. NO FDA 483 ISSUED. SEVERAL VERBAL OBSERVATIONS DISCUSSED AND CORRECTED PRIOR TO THE CLOSE OUT. METHOD VALIDATION AND METHOD TRANSFER COMPLETED. RECOMMEND FIRM AS ACCEPTABLE.				INSPECTION	
OC RECOMMENDATION	16-NOV-2011			ACCEPTABLE	SMITHDE
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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

(b) (4)

DMF No: **AADA:** I 074573

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Establishment Comment: DRUG SUBSTANCE MANUFACTURE, LOT RELEASE TESTING, ALTERNATE STABILITY TESTING SITE (on 12-SEP-2011 by T. LAMBERT () 301-796-4246)

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	20-SEP-2011				LAMBERTTU
SUBMITTED TO DO	20-SEP-2011	Product Specific			INYARDA
NEW MOLECULAR ENTITY					
DO RECOMMENDATION	21-SEP-2011			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	23-SEP-2011			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: DRUG SUBSTANCE (b) (4) TESTING BY ICP-MS FOR LOT RELEASE (on 12-SEP-2011 by T. LAMBERT () 301-796-4246)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	20-SEP-2011				LAMBERTTU
SUBMITTED TO DO	20-SEP-2011	Product Specific			INYARDA
NEW MOLECULAR ENTITY					
DO RECOMMENDATION	21-SEP-2011			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	23-SEP-2011			ACCEPTABLE	INYARDA
				DISTRICT RECOMMENDATION	

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/s/

NIKOO N MANOCHEHRI KALANTARI
02/02/2012