CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204114Orig1s000

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 204114, Mekinist™ (trametinib); 0.5 mg, 1 mg, and 2 mg Tablets

Date: 28-MAY-2013

Introduction

Trametinib dimethyl sulfoxide is a new molecular entity. The drug product is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations. It is a well-characterized crystalline solid (1:1 stoichiometric DMSO solvate) where DMSO is fully incorporated into the (b) (4) Quality by Design (QbD) element was utilized by the sponsor for the drug substance development based on the principals of ICHQ8 and Q9 regarding the impact of excipient properties on (b) (4).

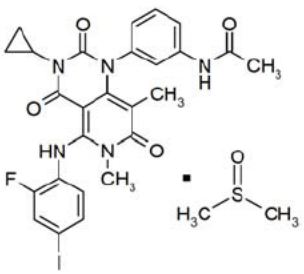
The drug product is an immediate release, film-coated tablet for oral administration containing trametinib dimethyl sulfoxide equivalent to 0.5 mg, 1 mg, or 2 mg of trametinib.

ONDQA recommends an approval action for this NDA. All CMC-related reviews/issues were completed and found acceptable including acceptable recommendation from office of compliance.

Summary

Chemical Name: Acetamide, N-[3-[3-cyclopropyl-5-[(2-fluoro-4- iodophenyl)amino]-3,4,6,7-tetrahydro-6,8-dimethyl-2,4,7-trioxopyrido[4,3-*d*]pyrimidin-1(2*H*)-yl]phenyl]-, compound with 1,1'-sulfinylbis[methane] (1:1)

Chemical Structure:



Molecular formula: $C_{26}H_{23}FIN_5O_4 \bullet C_2H_6OS$
Molecular weight: 693.53 (DMSO solvate of parent)
(b) (4) (non-solvated parent)

Trametinib dimethyl sulfoxide, a well-characterized crystalline solid, is a 1:1 stoichiometric DMSO solvate, where DMSO is fully incorporated into the (b) (4) (b) (4) The proposed drug substance commercial process

[redacted] The Critical Quality Attributes (CQAs) of trametinib dimethyl sulfoxide are included in the drug substance specification including description, identification, solid state form, trametinib content, chemical purity (including named impurities), DMSO content, residual solvents, water content, residue on ignition, heavy metal and particle size. Based on the stability data presented in the NDA dossier, an initial retest period of [redacted] is granted for Trametinib Dimethyl Sulfoxide drug substance.

The drug product is an immediate release, film-coated tablet for oral administration containing trametinib dimethyl sulfoxide equivalent to 0.5 mg, 1 mg, or 2 mg of trametinib (non-solvated parent). The compositions of the 0.5 mg, 1 mg, and 2 mg strengths [redacted] The drug product is a low dose tablet manufactured [redacted] The applicant addressed the issues in the application as well as with submissions to the Office of Compliance with [redacted] in accordance with cGMP requirements.

Chemistry, Manufacturing and Controls (CMC) Review #1 identified significant and numerous deficiencies related to both the drug substance and drug product during the review process (see CMC Review #1, pages 98-102 including ONDQA Biopharmaceutics IR issues related to specifications, shelf life and manufacturing process). However, all of these deficiencies were satisfactorily addressed by the sponsor. Four CMC information request (IR) letters have been conveyed to the applicant. All of the issues were addressed adequately during CMC review #1, with the exception of drug product stability issues. [redacted] the applicant proposed to change the storage condition to refrigerated temperature. The stability data for the drug product stored at refrigerated temperature, as submitted in the 12-Apr-2013 amendment (CMC review #2) which showed a [redacted]. Based on the stability data submitted in the above amendment, a 12-month expiration dating period is granted for the 0.5 mg and 2 mg tablets and a 9-month expiration dating period is granted for the 1 mg tablets when stored at 2° to 8°C (36°F to 46°F) and protected from moisture and light.

I concur with the approval recommendation for this NDA from a CMC perspective.

Ali Al-Hakim, Ph.D.
Branch II Chief, Division I
Office of New Drug Quality Assessment
CDER-FDA
Tel: 301 976 1323


(b) (4)

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

/s/

ALI H AL HAKIM
05/28/2013
Ali Al-Hakim for Sarah Pope Miksinski

NDA 204114

Mekinist™ (trametinib) Tablets

GlaxoSmithKline LLC

Review of Drug Product Sections
CMC Review #2

Sue-Ching Lin

Review Chemist

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

Chemistry, Manufacturing, and Controls (CMC)
Team Review of Original NDA
For the Division of Drug Oncology Products 2

Table of Contents

CMC Review Data Sheet

1. NDA 204114

2. REVIEW #: 2

3. REVIEW DATE: 10-May-2013

4. REVIEWER: Sue-Ching Lin

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
CMC Review #1 for this NDA	08-Apr-2013
Original NDA Submission	02-Aug-2012
Amendments previously reviewed in CMC Review #1	See CMC review #1

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed	DARRTS SD Number	Document Date	Stamp Date
Amendment (complete stability data, including data for the newly proposed refrigerated storage temperature, and revised labeling)	56	12-Apr-2013	12-Apr-2013
Amendment (revised container labels in response to the FDA 5/3/13 comments)	59	07-May-2013	07-May-2013

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	GlaxoSmithKline LLC
Address:	One Franklin Plaza, 200 North 16th Street Philadelphia, PA 19102
Representative:	Eric Richards, M.S., M.P.H., Director GRA 1250 South Collegeville Road, PA 19426
Telephone:	610-917-6842

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Mekinist™ Tablets
b) Non-Proprietary Name: trametinib tablets
c) Code Name/# (ONDQA only): GSK1120212
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1 (new molecular entity)
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: antineoplastic

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 0.5 mg, 1 mg, and 2 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

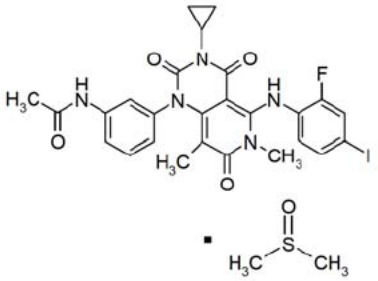
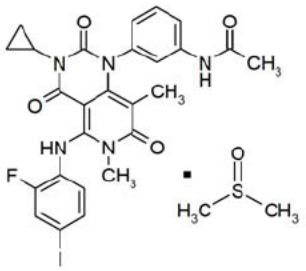
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__√__Not a SPOTS product

CMC Review Data Sheet

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

Chemical structure	
GlaxoSmithKline's representation of the chemical structure, used alternatively in the NDA	
Molecular formula	$C_{26}H_{23}FIN_5O_4 \cdot C_2H_6OS$
Molecular weight	693.53 (DMSO solvate of parent) (b) (4) (non-solvated parent)
United States Adopted Name (USAN)	trametinib dimethyl sulfoxide trametinib (non-solvated parent)
CAS Chemical name	Acetamide, N-[3-[3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-3,4,6,7-tetrahydro-6,8-dimethyl-2,4,7-trioxopyrido[4,3-*d*]pyrimidin-1(2*H*)-yl]phenyl]-, compound with 1,1'-sulfinylbis[methane] (1:1)
Chemical Abstracts Service (CAS) registry number	871700-17-3 (for non-solvated parent) 1187431-43-1 (for DMSO solvate)
GSK Laboratory Code	GSK1120212A (also referred to as GSK1120212) for the non-solvated parent GSK1120212B (for dimethyl sulfoxide solvate)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)		4	N/A	N/A	See Section 3.2.P.4
	III			4	N/A	N/A	See Section 3.2.P.7
	III			4	N/A	N/A	See Section 3.2.P.7
	III			4	N/A	N/A	See Section 3.2.P.7
	III			4	N/A	N/A	See Section 3.2.P.7
	III			3	Adequate	21-Mar-2012	Reviewed by Gene Holbert
	III			4	N/A	N/A	See Section 3.2.P.7

[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)

CMC Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	102175	Trametinib for Treatment of Subjects with Solid Tumors or Lymphoma
IND	113557	Trametinib for Treatment of BRAF Mutation Positive Melanoma

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	09-May-2013	J. Williams
Pharm/Tox	Acceptance criteria for impurities and DMSO higher limit are acceptable.	24-Oct-2012 & 19-Dec-2012	Sachia Khasar
Biopharm	Recommended for approval	05-Apr-2013	Minerva Hughes
LNC*	N/A		
Methods Validation	Acceptable	02-Mar-2013 and 29-Mar-2013	Jamie D. Dunn and Michael Trehy
DMEPA**	The proposed proprietary name "Mekinist" is acceptable.	19-Sep-2012	James H. Schlick
EA	Categorical exclusion (see review)	Date of this review	Sue-Ching Lin
Microbiology	Approval from microbiology product quality standpoint	30-Nov-2012	John W. Metcalfe

*LNC: Labeling and Nomenclature Committee
**DMEPA: Division of Medication Error Prevention and Analysis

CMC Review #2 for NDA 204114

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of chemistry, manufacturing, and controls, this NDA is recommended for approval.

Include the following language in the approval letter:

Based on the provided stability data, a 12-month expiration dating period is granted for the 0.5 mg and 2 mg tablets and a 9-month expiration dating period is granted for the 1 mg tablets when stored at 2° to 8°C (36°F to 46°F) and protected from moisture and light.

We acknowledge your commitment provided in the submission dated April 12, 2013 to place all future commercial batches on stability to provide concurrent monitoring at 5°C and to notify FDA of any changes to this protocol. Please note that a prior approval supplement will need to be submitted to revise this commitment. Refer to "Guidance for Industry, Changes to an Approved NDA or ANDA, April 2004."

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

None

II. Summary of CMC Assessments

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

(1) Drug Substance

Trametinib dimethyl sulfoxide, a well-characterized crystalline solid, is a 1:1 stoichiometric DMSO solvate, where DMSO is fully incorporated into the (b) (4) (b) (4) The proposed drug substance commercial process The

sponsor has adopted a Quality by Design (QbD) based concept for drug substance development based on the principals of ICHQ8 and Q9. However, there are not too much QbD data provided in the submission.

The Critical Quality Attributes (CQAs) of trametinib dimethyl sulfoxide are included in the drug substance specification including description, identification, solid state form, trametinib content, chemical purity (including named impurities), DMSO content, residual solvents, water content, residue on ignition, heavy metal and particle size.

Twenty-four months of stability data are presented for three batches of trametinib dimethyl sulfoxide manufactured at the proposed commercial site, GSK Jurong, and (b) (4) utilizing a process representative of the commercial process. Based on the stability data presented in the NDA dossier, an initial retest period of (b) (4) is granted for Trametinib Dimethyl Sulfoxide drug substance packaged (b) (4)

(2) Drug Product

The drug product is an immediate release, film-coated tablet for oral administration containing trametinib dimethyl sulfoxide equivalent to 0.5 mg, 1 mg, or 2 mg of trametinib (non-solvated parent). The compositions of the 0.5 mg, 1 mg, and 2 mg strengths (b) (4)

The drug product is a low dose tablet manufactured (b) (4) . The applicant addressed the issues in the application as well as with submissions to the Office of Compliance with (b) (4) in accordance with cGMP requirements.

(b) (4) the applicant proposed to change the storage condition to refrigerated temperature. The stability data for the drug product stored at refrigerated temperature, as submitted in the 12-Apr-2013 amendment, show a (b) (4) .

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

Mekinist is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test indicated for this use, who have not received BRAF inhibitor therapy.

The recommended daily dose is 2 mg. [redacted] (b) (4)

[redacted] Do not take a missed dose within 12 hours of the next dose.

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been provided for the manufacture and controls of the drug substance and drug product. The Microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective.

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed proprietary name Mekinist.

A methods validation consult was sent to the FDA St. Louis Laboratory for the drug substance and drug product analysis. The FDA laboratory has completed methods validation and found the methods to be acceptable for quality control and regulatory purposes.

The CMC revisions of the package insert have been incorporated into the revised labeling during the labeling meetings of the NDA. The revised container labels, as amended by the applicant on 07-May-2013, are acceptable from the CMC perspective.

The Office of Compliance has issued an overall "acceptable" recommendation dated 09-May-2013 for all facilities used for manufacturing and control of the drug substance and drug product.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Sue-Ching Lin, M.S., R.Ph., Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Nallaperumal Chidambaram, Ph.D., Acting Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

C. CC Block: entered electronically in DARRTS

12 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SUE CHING LIN
05/10/2013

NALLAPERUM CHIDAMBARAM
05/10/2013
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 6, 2013

From: Norma Griffin, Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 204114: CMC Team Leader Reviews

Dr. Nallaperumal Chidambaram signed off on Drs. Sue Ching Lin and Zhe J. Tang's April 8, 2013, review as a complete review.

NDA 204114

Mekinist (trametinib) Tablets

GlaxoSmithKline LLC

Review of Drug Product Sections

Sue-Ching Lin

Review Chemist

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

Chemistry, Manufacturing, and Controls (CMC)
Team Review of Original NDA
For the Division of Drug Oncology Products 2

Table of Contents

CMC Review Data Sheet

1. NDA 204114

2. REVIEW #: 1

3. REVIEW DATE: 08-Apr-2013

4. REVIEWER: Sue-Ching Lin

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 102175 submission	15-Apr-2008
Original IND 102175 CMC review	29-May-2008
CMC pre-Phase 3 meeting	09-Nov-2010
CMC-only pre-NDA meeting	15-Feb-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
CMC Pre-submission	0	02-Jul-2012	02-Jul-2012
Original NDA Submission	2	02-Aug-2012	03-Aug-2012
Revised FDA Form 356h for establishment information	7	21-Aug-2012	21-Aug-2012
Response to DMEPA 9/21/12 IR (b) (4)	14	25-Sep-2012	25-Sep-2012
Response to 9/19/12 Microbiology IR, updating stability specification with microbial limit testing	16	28-Sep-2012	28-Sep-2012
Response to FDA 9/27/12 CMC IR for container closure, etc.	18	11-Oct-2012	11-Oct-2012
Container sample label for 2 mg (b) (4)	19	26-Oct-2012	26-Oct-2012
Response to DMEPA 11/7/12 IR. There are no (b) (4)	24	07-Nov-2012	07-Nov-2012
Response to Biopharm 11/21/12 IR	29	07-Dec-2012	07-Dec-2012
Response to 12/05/12 IR	30	14-Dec-2012	14-Dec-2012
Response to CMC request in 12/19/12 telecon	32	16-Jan-2013	16-Jan-2013
Amendment (Proposal to change stability storage conditions to refrigerated temperature)	34	06-Feb-2013	06-Feb-2013
Amendment (Revised drug product specification)	37	27-Feb-2013	27-Feb-2013
Amendment (updated stability data)	40	05-Mar-2013	05-Mar-2013

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	GlaxoSmithKline LLC
Address:	One Franklin Plaza, 200 North 16th Street Philadelphia, PA 19102
Representative:	Eric Richards, M.S., M.P.H., Director GRA 1250 South Collegeville Road, PA 19426
Telephone:	610-917-6842

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Mekinist™ Tablets
b) Non-Proprietary Name: trametinib tablets
c) Code Name/# (ONDQA only): GSK1120212
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1 (new molecular entity)
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: antineoplastic

11. DOSAGE FORM: tablet

12. STRENGTH/POTENCY: 0.5 mg, 1 mg, and 2 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: __√__Rx ___OTC

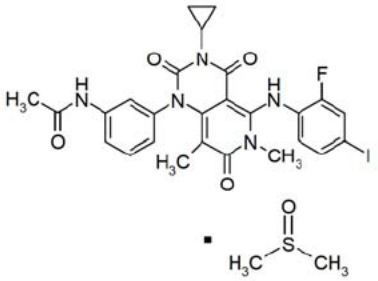
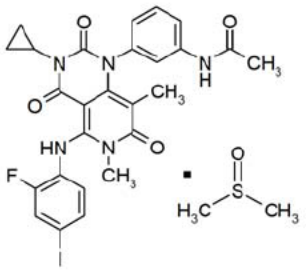
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__√___Not a SPOTS product

CMC Review Data Sheet

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

Chemical structure	
GlaxoSmithKline's representation of the chemical structure, used alternatively in the NDA	
Molecular formula	$C_{26}H_{23}FIN_5O_4 \cdot C_2H_6OS$
Molecular weight	693.53 (DMSO solvate of parent) (b) (4) (non-solvated parent)
United States Adopted Name (USAN)	trametinib dimethyl sulfoxide trametinib (non-solvated parent)
CAS Chemical name	Acetamide, N-[3-[3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-3,4,6,7-tetrahydro-6,8-dimethyl-2,4,7-trioxopyrido[4,3-*d*]pyrimidin-1(2*H*)-yl]phenyl]-, compound with 1,1'-sulfinylbis[methane] (1:1)
Chemical Abstracts Service (CAS) registry number	871700-17-3 (for non-solvated parent) 1187431-43-1 (for DMSO solvate)
GSK Laboratory Code	GSK1120212A (also referred to as GSK1120212) for the non-solvated parent GSK1120212B (for dimethyl sulfoxide solvate)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)		4	N/A	N/A	See Section 3.2.P.4
	III			4	N/A	N/A	See Section 3.2.P.7
	III			4	N/A	N/A	See Section 3.2.P.7
	III			4	N/A	N/A	See Section 3.2.P.7
	III			4	N/A	N/A	See Section 3.2.P.7
	III			3	Adequate	21-Mar-2012	Reviewed by Gene Holbert
	III			4	N/A	N/A	See Section 3.2.P.7

[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	102175	Trametinib for Treatment of Subjects with Solid Tumors or Lymphoma
IND	113557	Trametinib for Treatment of BRAF Mutation Positive Melanoma

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	pending		
Pharm/Tox	Acceptance criteria for impurities and DMSO higher limit are acceptable.	24-Oct-2012 & 19-Dec-2012	Sachia Khasar
Biopharm	Recommended for approval	05-Apr-2013	Minerva Hughes
LNC*	N/A		
Methods Validation	Acceptable	02-Mar-2013 and 29-Mar-2013	Jamie D. Dunn and Michael Trehy
DMEPA**	The proposed proprietary name "Mekinist" is acceptable.	19-Sep-2012	James H. Schlick
EA	Categorical exclusion (see review)	Date of this review	Sue-Ching Lin
Microbiology	Approval from microbiology product quality standpoint	30-Nov-2012	John W. Metcalfe

*LNC: Labeling and Nomenclature Committee
**DMEPA: Division of Medication Error Prevention and Analysis

The CMC Review for NDA 204114

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of chemistry, manufacturing, and controls, this NDA may be approved, pending satisfactory resolution of the issues noted below:

- An "acceptable" overall recommendation from the Office of Compliance for the inspections of the manufacturing and testing facilities for the drug substance and drug product
- Adequate stability data to support the newly proposed refrigerated storage conditions
- Acceptable container labels that includes newly proposed refrigerated condition and revised according to DMEPA comments.

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

None

II. Summary of CMC Assessments

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

(1) Drug Substance

Trametinib dimethyl sulfoxide, a well-characterized crystalline solid, is a 1:1 stoichiometric DMSO solvate, where DMSO is fully incorporated into the (b) (4) The proposed drug substance commercial process (b) (4) The sponsor has adopted a Quality by Design (QbD) based concept for drug substance development based on the principals of ICHQ8 and Q9. However, there are not too much QbD data provided in the submission.

The Critical Quality Attributes (CQAs) of trametinib dimethyl sulfoxide are included in the drug substance specification including description, identification, solid state form, trametinib content, chemical purity (including named impurities), DMSO content, residual solvents, water content, residue on ignition, heavy metal and particle size.

Twenty-four months of stability data are presented for three batches of trametinib dimethyl sulfoxide manufactured at the proposed commercial site, GSK Jurong, and (b) (4) utilizing a process representative of the commercial process. Based on the stability data presented in the NDA dossier, an initial retest period of (b) (4) is granted for Trametinib Dimethyl Sulfoxide drug substance packaged (b) (4)

(2) Drug Product

The drug product is an immediate release, film-coated tablet for oral administration containing trametinib dimethyl sulfoxide equivalent to 0.5 mg, 1 mg or 2 mg of trametinib (non-solvated parent). The compositions of the 0.5 mg, 1 mg, and 2 mg strengths (b) (4) . (b) (4)

The drug product is a low dose tablet manufactured (b) (4) The applicant provided historical data (about 22 batches) at commercial scale that show acceptable content and (b) (4) . The factors affecting (b) (4) are tightly controlled, (b) (4) . Dr. Sharmista Chatterjee (ONDQA QbD Lead) was consulted and she determined that the risk for achieving inhomogeneity in finished product is well mitigated. However, during a follow-up meeting with the ONDQA review team after the drug product inspection, the Office of Compliance (OC) expressed concerns about sampling plan and content uniformity. Through the combined efforts by the ONDQA and OC review teams, a Request for Additional Information (RAI) letter was conveyed to the applicant on 14-Feb-2013 requesting the company to demonstrate adequacy of mixing for commercial batches in accordance with 21 CFR 211.110 (e.g., blend homogeneity, stratified sampling using statistically representative sample size). As of the date of this review, the Office of Compliance has not issued a final recommendation for the inspection of the drug product manufacturing site.

The stability data show a (b) (4) at controlled room temperature. Due to the stability failures observed in the production batches as well as GSK's request to change the storage conditions to refrigerated temperature, the shelf-life determination is not considered in this review. GSK proposed to assemble a new stability package to justify for the refrigerated storage condition, which is expected to be submitted to the FDA by April 15, 2013.

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

Mekinist is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test indicated for this use, who have not received BRAF inhibitor therapy.

The recommended daily dose is 2 mg. (b) (4) Do not take a missed dose within 12 hours of the next dose.

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been provided for the manufacture and controls of the drug substance and drug product. The Microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective.

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed proprietary name Mekinist.

A methods validation consult was sent to the FDA St. Louis Laboratory for the drug substance and drug product analysis. The FDA laboratory has completed methods validation and found the methods to be acceptable for quality control and regulatory purposes. Due to a tightened acceptance criterion for dissolution test, the Biopharm reviewer has asked the FDA laboratory to verify that the revised dissolution sampling time is acceptable. The re-verification of the dissolution method has been completed by the FDA laboratories and the method was found acceptable. Refer to the 29-Mar-2013 method validation review.

The CMC revisions of the package insert have been incorporated into the revised labeling during the labeling meetings of the NDA. The revised container labels, as amended by the applicant on 14-Dec-2012 are acceptable from the CMC perspective with the exception that the storage condition will need to be revised according to the newly proposed refrigerated condition. The DMEPA comments for the container labeling were conveyed to the applicant on 20-Mar-2013. In response, the applicant revised the container labeling in the 26-Mar-2013 amendment, which is pending DMEPA review.

The Office of Compliance has not issued an overall recommendation for the inspections of the manufacturing and testing facilities for the drug substance and drug product. Therefore, this NDA may not be approved until a final acceptable recommendation is made by the Office of Compliance.

Due to drug product stability failure (b) (4) when stored at controlled room temperature, the applicant proposed to change the storage condition to

refrigerated temperature. This NDA can not be approved until adequate data are provided to support the newly proposed storage conditions.

III. Administrative

A. Reviewer's Signature:
(See appended electronic signature page)

Sue-Ching Lin, M.S., R.Ph., Reviewer, ONDQA

B. Endorsement Block:
(See appended electronic signature page)

Nallaperumal Chidambaram, Ph.D., Acting Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

C. CC Block: entered electronically in DARRTS

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/s/

SUE CHING LIN
04/08/2013

NALLAPERUM CHIDAMBARAM
04/08/2013
I concur.

NDA 204114

Mekinist™ (Trametinib) Tablets
0.5 mg, 1 mg and 2 mg

GlaxoSmithKline LLC

Z. Jean Tang, Ph.D

Review Chemist

Division of New Drug Quality Assessment Division I
Branch II

CMC REVIEW OF NDA 204114 DRUG SUBSTANCE
For the Division of Drug Oncology Products 2

Table of Contents

CMC Review Data Sheet

1. NDA 204-114

2. REVIEW #: 1

3. REVIEW DATE: 08-Apr-2013

4. REVIEWER: Z. Jean Tang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 102175 / 113557 Submission	14-APR-2008 / 29-MAR-2012
Original IND CMC review by	
IND 102175	Debasis Ghosh (29-MAY-2008)
IND 113557	Xiao H Chen (14-APR-2012)
CMC only pre-Phase 3 meeting	29-Nov-2010
CMC only pre-NDA meeting	15-Feb-2012

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

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
CMC Pre-submission	0	02-Jul-2012	02-Jul-2012
Original NDA Submission	2	02-Aug-2012	03-Aug-2012
Revised FDA Form 356h for establishment information	7	21-Aug-2012	21-Aug-2012
Response to DMEPA 9/21/12 IR to [redacted] (b) (4)	14	25-Sep-2012	25-Sep-2012
Response to 9/19/12 Microbiology IR, updating stability specification with microbial limit testing	16	28-Sep-2012	28-Sep-2012
Response to FDA 9/27/12 CMC IR for container closure, etc.	18	11-Oct-2012	11-Oct-2012
Container sample label for 2 mg [redacted] (b) (4)	19	26-Oct-2012	26-Oct-2012
Response to DMEPA 11/7/12 IR. There are no [redacted] (b) (4)	24	07-Nov-2012	07-Nov-2012
Response to Biopharm 11/21/12 IR	29	07-Dec-2012	07-Dec-2012
Response to 12/05/12 IR	30	14-Dec-2012	14-Dec-2012
Response to CMC request in 12/19/12 telecon	32	16-Jan-2013	16-Jan-2013
Amendment (Proposal to change stability storage conditions to refrigerated temperature)	34	06-Feb-2013	06-Feb-2013
Amendment (Revised drug product specification)	37	27-Feb-2013	27-Feb-2013
Amendment (updated stability data)	40	05-Mar-2013	05-Mar-2013

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	GlaxoSmithKline LLC
Address:	One Franklin Plaza, 200 North 16th Street Philadelphia, PA 19102
Representative:	Eric Richard, Global Regulatory Affairs 1250 South Collegeville Road, PA 19426
Telephone:	1-888-825-5249

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: MEKINIST™
b) Non-Proprietary Name: Trametinib
c) Code Name/# (ONDQA only): GSK1120212
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1 New Molecular Entity
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: Anti-cancer

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 0.5 mg, 1 mg and 2 mg

13. ROUTE OF ADMINISTRATION: Oral

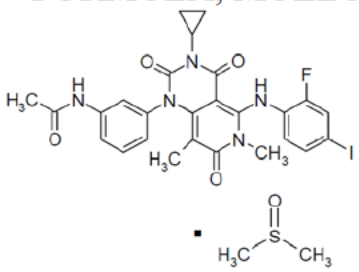
14. Rx/OTC DISPENSED: _X_Rx ___OTC

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:

IUPAC: Equimolecular combination of N-(3-{3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl}phenyl)acetamide with (methylsulfinyl)methane

CAS: Acetamide, N-[3-[3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-3,4,6,7-tetrahydro-6,8-dimethyl-2,4,7-trioxopyrido[4,3-*d*]pyrimidin-1(2*H*)-yl]phenyl]-,compound with 1,1'-sulfinylbis[methane] (1:1)

USAN: Trametinib dimethyl sulfoxide
Trametinib (non-solvated parent)

Molecular Formula: $C_{26}H_{23}FIN_5O_4 \cdot C_2H_6OS$

Molecular Weight: 693.53 g/mol ((DMSO solvate of parent)
(b) (4) g/mol (non-solvated parent)

Isomerism and Stereoisomerism: GSK1120212B possesses no chiral centers or olefinic double bonds and therefore has no potential for optical or geometrical isomerism.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

No DMF for drug substance.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	102175	Trametinib for Treatment of Subjects with Solid Tumors or Lymphoma
IND	113557	Trametinib for Treatment of BRAF Mutation Positive Melanoma

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	12-DEC-2011	
EES	Pending		
Drug Substance	Approvable	Date of this Review	Jean (Zhe) Tang
Drug Product	Approvable	Date of this Review	Sue Ching Lin
Pharm/Tox	Acceptance criteria for impurities and DMSO higher limit are acceptable	24-Oct-2012 & 19-Dec-2012	Gabriel S. Khasar
Biopharm	Recommended for approval	05-APR-2013	Minerva Hughes
Methods Validation	Acceptable	02-Mar-2013 and 29-Mar-2013	Michael Trehy and Jamie D. Dunn
LNC*	N/A		
DMEPA**	The proposed proprietary name "Mekinist" is acceptable.	19-Sep-2012	James H. Schlick
EA	Categorical exclusion (see review)	Date of this Review	Sue-Ching Lin
Microbiology	Approval from microbiology product quality standpoint	30-Nov-2012	John W. Metcalfe

*LNC: Labeling and Nomenclature Committee

**DMEPA: Division of Medication Error Prevention and Analysis

The Chemistry Review for NDA 204-114

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of chemistry, manufacturing, and controls, this NDA may be approved, pending satisfactory resolution of the issues noted below:

- An "acceptable" overall recommendation from the Office of Compliance for the inspection of the manufacturing and testing facilities for the drug substance and drug product
- Adequate stability data to support the newly proposed refrigerated storage conditions
- Acceptable container labels that includes newly proposed refrigerated condition and revised according to DMEPA comments.

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 Product(s) and Drug Substance(s)

DRUG SUBSTANCE

Trametinib dimethyl sulfoxide, a well-characterized crystalline solid, is a 1:1 stoichiometric DMSO solvate, where DMSO is fully incorporated into the (b) (4) (b) (4) . The proposed drug substance commercial process

The sponsor has adopted a Quality by Design (QbD) based concept for drug substance development based on the principals of ICHQ8 and Q9. However, there are not too much QbD data provided in the submission.

The Critical Quality Attributes (CQAs) of trametinib dimethyl sulfoxide are included in the drug substance specification including description, identification, solid state form, trametinib content, chemical purity (including named impurities), DMSO content, residual solvents, water content, residue on ignition, heavy metal and particle size.

Twenty four months of stability data are presented for three batches of trametinib dimethyl sulfoxide manufactured at the proposed commercial site, GSK Jurong, and (b) (4) utilizing a process representative of the commercial process. Based on the stability data presented in the NDA dossier, an initial retest period of (b) (4) is granted for Trametinib Dimethyl Sulfoxide drug substance (b) (4)

As of the date of this review, the Office of Compliance has not issued a final recommendation for the inspection of the drug substance manufacturing site.

(2) Drug Product

The drug product is an immediate release, film-coated tablet for oral administration containing trametinib dimethyl sulfoxide equivalent to 0.5 mg, 1 mg or 2 mg of trametinib (non-solvated parent). The compositions of the 0.5 mg, 1 mg, and 2 mg strengths (b) (4)

The drug product is a low dose tablet manufactured (b) (4) The applicant provided historical data (about 22 batches) at commercial scale that show acceptable content and (b) (4). The factors affecting (b) (4) . Dr. Sharmista Chatterjee (ONDQA QbD Lead) was consulted and she determined that the risk for achieving inhomogeneity in finished product is well mitigated. However, during a follow-up meeting with the ONDQA review team after the drug product inspection, the Office of Compliance (OC) expressed concerns about sampling plan and content uniformity. Through the combined efforts by the ONDQA and OC review teams, a Request for Additional Information (RAI) letter was conveyed to the applicant on 14-Feb-2013 requesting the company to demonstrate adequacy of mixing for commercial batches in accordance with 21 CFR 211.110 (e.g., blend homogeneity, stratified sampling using statistically representative sample size). As of the date of this review, the Office of Compliance has not issued a final recommendation for the inspection of the drug product manufacturing site.

The stability data show a (b) (4) when stored at controlled room temperature. Due to the stability failures observed in the production batches as well as GSK's request to change the storage conditions to refrigerated temperature, the shelf-life determination is not considered in this review.

GSK proposed to assemble a new stability package to justify for the refrigerated storage condition, which is expected to be submitted to the FDA by April 15, 2013.

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

Mekinist is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test indicated for this use, who have not received BRAF inhibitor therapy.

The recommended daily dose is 2 mg. (b) (4) Do not take a missed dose within 12 hours of the next dose.

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been provided for the manufacture and controls of the drug substance and drug product. The Microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective.

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed proprietary name Mekinist.

A methods validation consult was sent to the FDA St. Louis Laboratory for the drug substance and drug product analysis. The FDA laboratory has completed methods validation and found the methods to be acceptable for quality control and regulatory purposes. Due to a tightened acceptance criterion for dissolution test, the Biopharm reviewer has asked the FDA laboratory to verify that the revised dissolution sampling time is acceptable. The re-verification of the dissolution method has been completed by the FDA laboratories and the method was found acceptable. Refer to the 29-Mar-2013 method validation review.

The CMC revisions of the package insert have been incorporated into the revised labeling during the labeling meetings of the NDA. The revised container labels, as amended by the applicant on 14-Dec-2012 are acceptable from the CMC perspective with the exception that the storage condition will need to be revised according to the newly proposed refrigerated condition. The DMEPA comments for the container labeling were conveyed to the applicant on 20-Mar-2013. In response, the applicant revised the container labeling in the 26-Mar-2013 amendment, which is pending DMEPA review.

The Office of Compliance has not issued an overall recommendation for the inspections of the manufacturing and testing facilities for the drug substance and drug product. Therefore, this NDA may not be approved until a final acceptable recommendation is made by the Office of Compliance.

(b) (4)
the applicant proposed to change the storage condition to refrigerated temperature. This NDA can not be approved until adequate data are provided to support the newly proposed storage conditions.

III. Administrative

A. Reviewer's Signature

(See appended electronic signature page)

Z. Jean Tang, Ph.D.
CMC Reviewer
Branch II, Division I, ONDQA
CDER, FDA

B. Endorsement Block

(See appended electronic signature page)

N. Chidambaram, Ph.D.
Acting Branch Chief
Branch III, Division I, ONDQA
CDER, FDA

C. CC Block entered electronically in DARRTS

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/s/

ZHE J TANG
04/08/2013

NALLAPERUM CHIDAMBARAM
04/08/2013
I concur.

PRODUCT QUALITY (Small Molecule)
FILING REVIEW and IQA FOR NDA ~~or Supplement~~ (ONDQA)

NDA Number: 204-114	**Supplement Number and Type:**	**Established/Proper Name:** Trametinib dimethylsulfoxide
Applicant: GlaxoSmithKline(GSK), LLC	**Letter Date:** 03 August, 2012 (~~Resubmission~~)	**Stamp Date:** 03 August, 2012

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	Yes		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	Yes		
3.	Are all the pages in the CMC section legible?	Yes		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	Yes		Type B CMC Meeting was held on November 9, 2010 . There are disagreements with starting material, etc Pre-NDA CMC meeting was held on February 15, 2012. Pre-NDA meeting was held on 09-May, 2012

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	Yes		Request via IR through ONDQA project Manager, Jewell Martin
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			N/A

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	Yes		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	Yes		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	Yes		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	Yes		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	Yes		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	Yes		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	Yes		
14.	Does the section contain information regarding the characterization of the DS?	Yes		
15.	Does the section contain controls for the DS?	Yes		
16.	Has stability data and analysis been provided for the drug substance?	Yes		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?	Yes		By ONDQA QbD Liaison, Dr. Anne Marie Russell. See my additional note
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		No	See also PQM Memo

PRODUCT QUALITY (Small Molecule)
FILING REVIEW and IQA FOR NDA ~~or Supplement~~ (ONDQA)

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	Yes		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	Yes		
21.	Is there a batch production record and a proposed master batch record?	Yes		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	Yes		
23.	Have any biowaivers been requested?			Fileable from ONDQA Biopharm. See Biopharm filing review in DARRTS.
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	Yes		
25.	Does the section contain controls of the final drug product?	Yes		
26.	Has stability data and analysis been provided to support the requested expiration date?			Review issue and Stat consult is needed
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	Yes		By ONDQA QbD Liaison, Dr. Anne Marie Russell. See my additional note and PQM Memo
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		No	ONDQA QbD Liaison, Dr. Anne Marie Russell. Refer to QPM Memo

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	Yes		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	Yes		Tablet No test is proposed

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	Yes		LOA provided

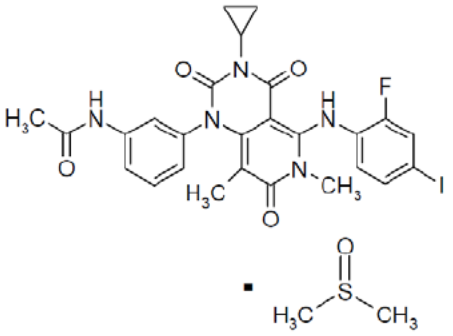
DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA PROVIDED?	COMMENTS
(b) (4)	III		(b) (4)	Yes	
	IV			Yes	
	III			Yes	
	III			Yes	
	III			Yes	
	III			Yes	
	III			Yes	
	III			Yes	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	Yes		
33.	Have the immediate container and carton labels been provided?	Yes		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	Yes		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	Yes		No CMC fileability issue. But, there are CMC IR and potential QbD IR
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		No	

Note: Trametinib (GSK1120212 and previously known as JTP-74057) is a new chemical entity and a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. MEK1 and MEK2 are proteins in this central signal transduction pathway and are critical for cell proliferation and survival. Oncogenic mutations in upstream proteins result in activation of this pathway and demonstrate its importance as a therapeutic target for solid tumors. This New Drug Application (NDA) is submitted for marketing approval of trametinib for the following indication (granted as Orphan drug indiction): Trametinib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation as detected by an FDA approved test.

The drug substance is the dimethyl sulfoxide (DMSO) solvate of trametinib, with the following chemical structure.



Trametinib DMSO was selected [redacted] (b) (4) The justification for the selected DMSO content ranges will be closely evaluated in conjunction with the assigned teams to ensure that clinically relevant ranges are established for product quality. The proposed drug product is an immediate-release tablet comprised of the drug substance and the excipients mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate (vegetable source), sodium lauryl sulfate, colloidal silicon dioxide. The tablets are available in three strengths (0.5, 1, and 2 mg), which are film-coated with a solution of hypromellose, titanium dioxide, polyethylene glycol, polysorbate 80 (2 mg tablets), iron oxide yellow (0.5 mg tablets), or iron oxide red (2 mg tablets).
The impact of these changes on in vitro tablet dissolution performance will be evaluated in the ONDQA Biopharmaceutics review.

- Appropriate dissolution method needs to be reviewed by ONDQA Biopharm team
- Defining acceptable DMSO content limits and limits should not be used ICHQ3C guidance for PDE [redacted] (b) (4)
- Need acceptance criteria for the quality of DMSO
- Total impurities and individual impurity acceptance criteria should be evaluated. It appears that acceptance criteria might need be tightened (also see Tox section).
- It appears that the applicant refers to ICHQ8, 9, 10, 11 guidances for DOE QbD in the submission. Thus, it contains Quality-by-Design (QbD) elements such as the identification of critical quality attributes (CQAs), risk assessments, proven acceptable ranges (PARs), and design

of experiment (DoE) studies. But, there are no actual data or models are specifically provided. The team will further evaluate it with this regard

- The chemical structure should be evaluated as the applicant claimed
- All sites for DS, DP and testing are already submitted into EES
- The statistical consult may need to be sent for the stability of DS and DP sections (refer to ICHQ1Dand ICHQ1E).
- No test for the microbial limit testing is proposed and this will be a review issues since DP might be moisture sensitive.
- [redacted] (b) (4) test and control need to evaluated with low solubility and strength tablets. The process should closely inspected including [redacted] (b) (4) stage.
- Heavy metal test, the applicant may test for ten batches as post-approval commitment.
- The CMC team review is recommended since this is designated as a priority NDA,

Liang Zhou *8-29-2012*

Name of
CMC Lead / ~~CMC Reviewer~~ Date
Division of Pre-Marketing Assessment # 1
Office of New Drug Quality Assessment

{ Nallaperum, Chidambaram} *8-29-2012*

Name of
Branch Chief Date
Division of Pre-Marketing Assessment # 1
Office of New Drug Quality Assessment

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

/s/

LIANG ZHOU
08/31/2012

NALLAPERUM CHIDAMBARAM
08/31/2012

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 204114/000	**Sponsor:**	GLAXOSMITHKLINE LLC
Org. Code:	107		1250 SOUTH COLLEGEVILLE RD UP4110
Priority:	1		COLLEGEVILLE, PA 19426
Stamp Date:	03-AUG-2012	**Brand Name:**	Trametinib
PDUFA Date:	03-SEP-2013	**Estab. Name:**	
Action Goal:		**Generic Name:**	Trametinib
District Goal:	05-JUL-2013	**Product Number; Dosage Form; Ingredient; Strengths**	001; TABLET; TRAMETINIB; (b) (4) 002; TABLET; TRAMETINIB; 003; TABLET; TRAMETINIB;

FDA Contacts:				
D. GHOSH	Prod Qual Reviewer	(HFD-150)	3017964093
J. METCALFE	Micro Reviewer	(HFD-805)	3017961576
J. MARTIN	Product Quality PM	(HFV-530)	3017962072
N. GRIFFIN	Regulatory Project Mgr	(HFD-107)	3017964255
L. ZHOU	Team Leader		3017961781

Overall Recommendation:	ACCEPTABLE	on 09-MAY-2013	by J. WILLIAMS	()	3017964196
	PENDING	on 15-AUG-2012	by EES_PROD		

Establishment: **CFN:** 9611205 **FEI:** 3002807079

GLAXO WELLCOME MANUFACTURING PTE LIMITED
2262

JURONG, , SINGAPORE

Duns No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE (b) (4)

DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STABILITY TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-MAR-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 1033964 **FEI:** 1033964		
	GLAXOSMITHKLINE INC		
	ZEBULON, , UNITED STATES 275971217		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE PACKAGER		
	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	17-AUG-2012		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** 9612768 **FEI:** 3002807114		
	GLAXOSMITHKLINE MANUFACTURING S.P.A. 43056		
	SAN POLO DI TORRILE , PARMA, ITALY		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
	FINISHED DOSAGE RELEASE TESTER		
Profile:	TABLETS, PROMPT RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	09-MAY-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		