CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202806Orig1s000

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 202806, Tafinlar™ (dabrafenib) Capsules

Date: 28-MAY-2013

Introduction

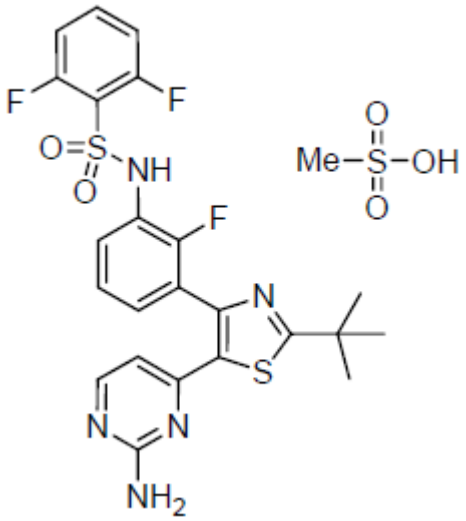
Dabrafenib is a new molecular entity and is manufactured as a mesylate salt. The proposed commercial drug product is an immediate release capsule dosage form available in two different strengths; 50 mg and 75 mg. Dabrafenib is an anticancer drug indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

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[1].

Summary

Chemical Name: Beezaesalfaaeaede, N-[3-[5-(2-amino-4- pyriaaidinyl)-2-(1,l-dimethylethyl)-4-thiazolyl]-2-fluorophenyl]-2,6-difluoro-, methanesulfonate salt

Chemical Structure:



Molecular formula: $C_{23}H_{20}F_3N_5O_2S_2 \cdot CH_4O_3S$
Molecular weight: 615.68 g/mol (dabrafenib mesylate)
519.57 g/mol (dabrafenib free base)

[1] See CMC memorandum in DARRTS dated May 02, 2013 regarding the acceptable recommendation given by office of compliance for the facilities and subsequent CMC approval recommendation for the NDA.

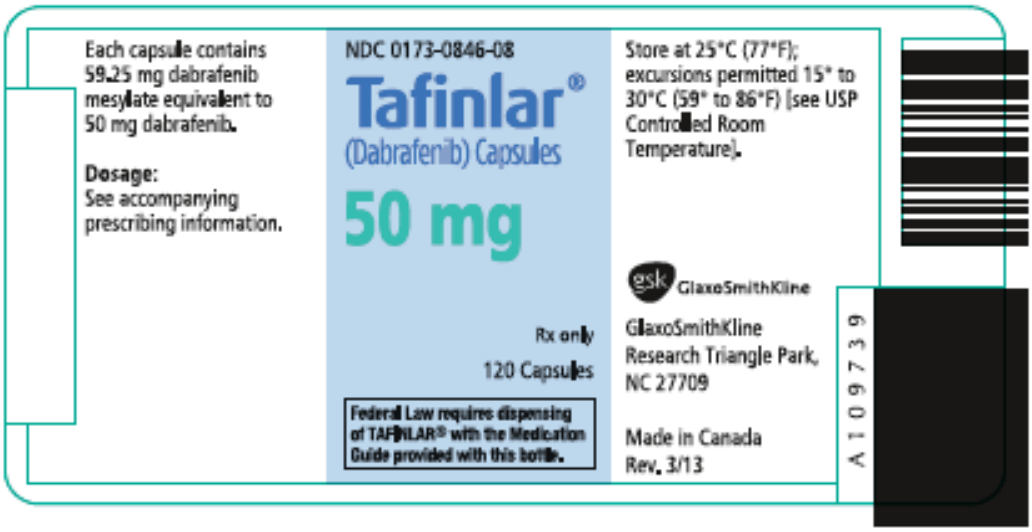
Dabrafenib mesylate drug substance is chemically synthesized from starting materials [redacted] The mesylate salt was selected because [redacted] Potential and actual impurities [redacted] were identified, characterized and controlled accordingly. A number of deficiencies, related to the manufacturing process of the drug substance, were identified and were communicated to the sponsor. However, these deficiencies were addressed adequately by sponsor as outlined in CMC review # 1.
Based on the stability data provided in the application, a retest period of [redacted] stored at a recommended room temperature conditions is granted for the drug substance.

The proposed commercial drug product, Tafinlar™ (dabrafenib), is an immediate release capsule dosage form available in two different strengths: 50 mg and 75 mg capsules. The drug product capsules are manufactured by [redacted]
Specifications (tests and limits) for the drug product were reviewed and found acceptable. [redacted] The sponsor provided the adequate control strategy for the functional properties of the excipinets used in the capsule formulation.
Based on the provided stability data, an expiration dating period of 24 months is granted for the drug product stored at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

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

Representative of the container label (for the 50 mg capsules)



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/s/

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

Memorandum

To: NDA 202-806

CC:

From: Amit K. Mitra, Ph.D

Through: Nallaperumal Chidambaram, Ph.D

Date: 5/2/2013

Re: Homogeneity of the entire batch and the OC recommendation

---

In the Chemistry Review #1, it was reported that the applicant was yet to implement a satisfactory control strategy to assure homogeneity of the entire batch during commercial manufacture as required by the GMP. Therefore, the OC did not grant an "Acceptable" recommendation for the facilities.

In an amendment, dated 26-APR-2013, the applicant adopted a satisfactory process control strategy using USP<905> acceptance criteria for the finished drug product and assay of individual capsules of the in-process samples with appropriate sampling plan. The control strategy adopted by the applicant is acceptable to the OC and the reviewer. Therefore, the OC has given an "Acceptable" recommendation for the facilities.

No other pending CMC issues remain for approval of this NDA.

Include 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 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

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/s/

AMIT K MITRA
05/02/2013

NALLAPERUM CHIDAMBARAM
05/02/2013
I concur

Memorandum

To: NDA 202806

CC:

From: Gaetan Ladouceur, Ph.D

Through: Nallaperumal Chidambaram, Ph.D

Date: 5/2/2013

Re: Homogeneity of the entire batch and the OC recommendation

---

In the Chemistry Review #1, it was reported that OC did not grant an "Acceptable" recommendation for the facilities. The issue was related to the implementation of a satisfactory control strategy to assure batch homogeneity during commercial manufacture of the drug product, as required by the GMP.

In an amendment, dated 26-APR-2013, the applicant adopted a satisfactory process control strategy using USP<905> acceptance criteria for the finished drug product and assay of individual capsules of the in-process samples with appropriate sampling plan. The control strategy adopted by the applicant is acceptable to the OC and the reviewer. Therefore, the OC has given an "Acceptable" recommendation for the facilities (see attachment on the following page).

No other pending CMC issues remain for approval of this NDA.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 202806/000
Org. Code: 107
Priority: 1
Stamp Date: 30-JUL-2012
PDUFA Date: 30-MAY-2013
Action Goal:
District Goal: 01-DEC-2012

Sponsor: GLAXOSMITHKLINE
200 NORTH 16TH ST 1 FRANKLIN PLAZA
PHILADELPHIA, PA 19102
Brand Name: Tafinlar
Estab. Name:
Generic Name: Dabrafenib
Product Number; Dosage Form; Ingredient; Strengths
001; CAPSULE; DABRAFENIB; EQ 50MG BASE
002; CAPSULE; DABRAFENIB; EQ 75MG BASE

FDA Contacts:				
	A. MITRA	Prod Qual Reviewer		3017961420
	B. RILEY	Micro Reviewer	(HFD-805)	3017961595
	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 30-APR-2013	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 02-APR-2013	by EES_ADMIN		
	ACCEPTABLE	on 14-MAR-2013	by STOCKM		
	PENDING	on 15-AUG-2012	by EES_PROD		
	PENDING	on 15-AUG-2012	by EES_PROD		

Establishment: **CFN:** 9611205 **FEI:** 3002807079
GLAXO WELLCOME MANUFACTURING PTE LIMITED
2262
JURONG, , SINGAPORE
DMF No: **AADA:**
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE (b) (4)
DRUG SUBSTANCE OTHER 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:** 9610421 **FEI:** 3002807078

GLAXOSMITHKLINE
HARMIRE ROAD

BARNARD CASTLE, COUNTY DURHAM, UNITED KINGDOM DL12 8DT

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-AUG-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** 1033964 **FEI:** 1033964

GLAXOSMITHKLINE INC

ZEBULON, , UNITED STATES 275971217

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

FINISHED DOSAGE STABILITY TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-AUG-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-AUG-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

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

GLAXOSMITHKLINE INC

(b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

FINISHED DOSAGE MANUFACTURER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 31-AUG-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MICRONIZER

DRUG SUBSTANCE OTHER TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-AUG-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

CROSSWAYS BOULEVARD

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MICRONIZER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-AUG-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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/s/

GAETAN LADOUCEUR
05/02/2013

NALLAPERUM CHIDAMBARAM
05/02/2013
I concur

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

Memorandum

Date: May 2, 2013

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

Subject: NDA 202806: CMC Team Leader Reviews

Dr. Nallaperumal Chidambaram signed off on Drs. Gaetan Laourceur and Amit Mitra's April 10, 2013, review as a complete review.

NDA 202-806

TAFINLAR

GlaxoSmithKline, LLC

Division of Oncology Drug Products

Drug Product Review

Amit K. Mitra, Ph.D

Branch II/ONDQA

Table of Contents

Chemistry Review Data Sheet

1. NDA or ANDA 202-806

2. REVIEW #:1

3. REVIEW DATE: 3-APR-2013

4. REVIEWER: Amit K. Mitra, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	21-JUN-2012
Amendment	30-AUG-2012
Amendment	04-FEB-2013
Amendment	27-MAR-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	GlaxoSmithKline, LLC
Address:	One Franklin Plaza, 200 North 6th Street, Philadelphia, PA 19102
Representative:	Ellen Cutler

Telephone: 610-917-6823

8. DRUG PRODUCT NAME/CODE/TYPE: Dabrafenib capsules

a) Proprietary Name: Tafinlar
b) Non-Proprietary Name (USAN): Dabrafenib mesylate
c) Code Name/# (ONDC only):GSK2118436B
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1S
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Antineoplastic (Unresectable or metastatic melanoma with a BRAF V600 mutation)

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 50 and 75 mg

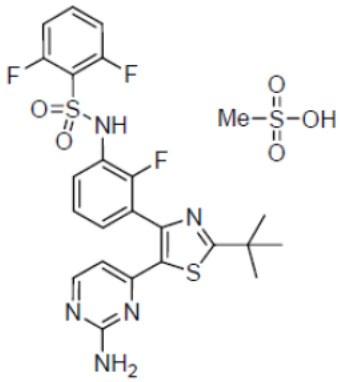
13. ROUTE OF ADMINISTRATION: Oral

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)	**Approved Name:**	
	USAN	Dabrafenib mesylate
	INN	Dabrafenib (r-INN)
	Chemical Name:	
	CAS Name	Benzenesulfonamide, *N*-[3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-4-thiazolyl]-2-fluorophenyl]-2,6-difluoro-, methanesulfonate (1:1)
	IUPAC Name	N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulfonamide, methanesulfonate salt
Empirical Formula	$C_{23}H_{20}F_3N_5O_2S_2 \cdot CH_4O_3S$	
Molecular Weight	615.68 g/mol (dabrafenib mesylate) 519.57 g/mol (dabrafenib free base)	
CAS Registry Number	1195768-06-9	
Structural Formula		

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	TYP	HOLDER	ITEM	CODE	STATUS	DATE	COMMENTS

Chemistry Review Data Sheet

#	E		REFERENCED	[1]	[2]	REVIEW COMPLETED	
(b) (4)	IV	(b) (4)	(b) (4)	1	Adequate	Dr. Amit K. Mitra	29-MAR-2013
	IV			3	Adequate	Dr. Zedong Dong	18-JAN-2012
	III			4			Adequate information is in the submission
	III			4			Adequate information is in the submission
	III			7	Adequate (Annual Report-16)	Dr. George Lunn	Since the last review (Annual Report 16) annual report 17 has been submitted. No additional information related to quality and safety of the desiccant was provided in the Annual Report 17. Therefore, the annual report was not reviewed
	III			4			Adequate information is in the submission
	III			4			Adequate information is in the submission
	III			4			Adequate information is in the submission

[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: None

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	02-APR-2013	
Pharm/Tox	N/A		
Biopharm	Acceptable	8-FEB-2013	AKM Khairuzzaman
LNC	Established name satisfactory		Amit K. Mitra
Methods Validation	Requested		Amit K Mitra
DMEPA	Satisfactory	12-FEB-2013	Sue H Kang
EA	Satisfactory	02-APR-2013	Amit K Mitra
Microbiology	Satisfactory	13-FEB-2013	Bryan S Riley

The Chemistry Review for NDA 202-806

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable pending resolution of facilities deficiencies.

Once OC provides acceptable recommendation for the facilities, include 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 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

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 Product: The proposed commercial drug product is an immediate release capsule dosage form available in two different strengths. The 50 mg capsules are dark red capsules imprinted with "GS TEW" and "50 mg"; whereas, 75 capsules are dark pink capsules imprinted with "GS LHF" and "75 mg".

Each 50 mg capsule contains 59.25 mg dabrafenib mesylate equivalent to 50 mg dabrafenib free base.

Dabrafenib Capsules, 75 mg, are opaque, (b) (4) capsules composed of a dark pink body and a dark pink cap. Each capsule, intended for oral administration, contains 88.88 mg of dabrafenib mesylate equivalent to 75 mg of dabrafenib free base.

The micronized dabrafenib mesylate drug substance is (b) (4) with microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate (b) (4) hydoxypropylmethylcellulose capsules (b) (4)

Upon request the sponsor provided the control strategy for the functional properties of the excipients and those are satisfactory according to the current regulatory standard.

Dabrafenib Capsules, 50 mg and 75 mg are packed with silica gel desiccant into opaque, white HDPE bottles, and closed with (b) (4), with a (b) (4) induction heat seal liner.

Dabrafenib Capsules were developed as simple immediate release capsule formulations. Initially, 1 mg, 5 mg, 25 mg, and 100 mg strengths of drug product capsules were developed to allow dosing flexibility in Phase 1 clinical trials. Later 50 mg and 75 mg strengths were developed to allow twice a day dosing of (b) (4) 150 mg. The formulations of all capsule strengths used in the clinic are presented below. The 50 mg and 75 mg strength capsules initially employed hard gelatin capsule shells. The hard gelatin capsule shells were replaced with hypromellose (HPMC) capsule shells (b) (4)

The Phase 3 study (BRF113683) and the Phase 2 study in brain metastases (BRF113929) used only hypromellose capsules.

The specification of the drug product includes: 1) Description, 2) ID for dabrafenib mesylate by UV and HPLC, 3) Content of dabrafenib by HPLC, 4) Uniformity of content by weight variation, and 5) Related substances by HPLC. (b) (4) . The microbial limits are being monitored at the first stability time point.

The applicant's current process control strategy for homogeneity using weight variation alone. This issue was consulted with the Office of Compliance (OC). The OC does not agree that the applicant's control strategy for homogeneity of the entire batch is adequate according to the 21CFR §211.110. The CMC reviewer does not believe (b) (4) Since the commercial scale (b) (4) is a GMP issue the OC has given a "Pending" recommendation for the facilities. For details see the review notes.

The applicant has provided adequate stability data for the tentative shelf life of 24 months.

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

The 50 mg Capsules are Dark red capsules imprinted with 'GS TEW' and '50 mg' and they are available in bottles of 120 (NDC 0173-0846-08). Each bottle contains a silica gel desiccant.

The 75 mg Capsules are Dark pink capsule imprinted with 'GS LHF' and '75 mg' available in bottles of 120 (NDC 0173-0847-08). Each bottle contains a silica gel desiccant.

C. Basis for Approvability or Not-Approval Recommendation

The OC has provided a pending recommendation for the facilities. The application is not recommended to be approved until the facilities are declared "Acceptable" by OC.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

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/s/

AMIT K MITRA
04/10/2013

NALLAPERUM CHIDAMBARAM
04/10/2013
I concur.

NDA 202806

Tafinlar™
(dabrafenib) Capsules

GSK

CMC Team Review:
Gaétan Ladouceur, Ph.D. (Drug Substance)

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

Table of Contents

CMC Review Data Sheet

1. NDA 202806

2. REVIEW #: 1

3. REVIEW DATE: 03-Apr-2013

4. REVIEWER: Gaetan Ladouceur, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original IND 105032 submission	29-Jun-2009
CMC Review # 1 (William Adams)	27-Aug-2009
Type C (CMC) Meeting Minutes	31-Jan-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date
Original NDA Submission	SD 000	21-Jun-2012
Amendment (SR 029)	SD 028	18-Dec-2012
Amendment (SR 034)	SD 033	14-Jan-2013
Amendment (SR 039)	SD 038	04-Feb-2012
Amendment (SR 053)	SD 051	02-Apr-2012

7. NAME & ADDRESS OF APPLICANT (last updated on 06-Jun-2012):

Name:	GlaxoSmithKline LLC
Address:	1250 South Collegeville Road Collegeville, PA 19426
Representative:	Ellen S. Cutler, Senior Director, Regulatory Affairs
Telephone:	610-917-6823

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Tafinlar ®
b) Non-Proprietary Name:	Dabrafenib
c) Code Name/# (ONDQA only):	NA
d) Chem. Type/Submission Priority (ONDQA only):	
• Chem. Type:	1
• Submission Priority:	S

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

10. PHARMACOL. CATEGORY: Anticancer

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 50 mg and 75 mg

13. ROUTE OF ADMINISTRATION: Oral

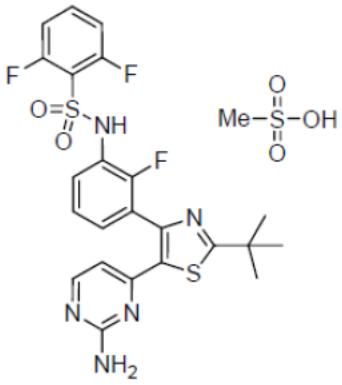
14. Rx/OTC DISPENSED: __√__ Rx ___ OTC

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

_____ SPOTS product – Form Completed

__√__ Not a SPOTS product

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

Chemical Name(s)	**Approved Name:**	
	USAN	Dabrafenib mesylate
	INN	Dabrafenib (r-INN)
	Chemical Name:	
	CAS Name	Benzenesulfonamide, *N*-[3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-4-thiazolyl]-2-fluorophenyl]-2,6-difluoro-, methanesulfonate (1:1)
	IUPAC Name	N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulfonamide, methanesulfonate salt
Empirical Formula	$C_{23}H_{20}F_3N_5O_2S_2 \cdot CH_4O_3S$	
Molecular Weight	615.68 g/mol (dabrafenib mesylate) 519.57 g/mol (dabrafenib free base)	
CAS Registry Number	1195768-06-9	
Structural Formula		

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: No DMF were provided in the DS section.

DMF #	TYPE	HOLDER	ITEM REFERENCED/ LOA DATE	CODE	STATUS	DATE REVIEW COMPLETED	COMMENTS
NA	NA	NA	NA	NA	NA	NA	NA

[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")

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	105032	Original IND

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Pending		Weishi Yuan
EES	Pending		Elizabeth Philpy
Pharm/Tox	Pending		Alexander Putman
Biopharm	Acceptable	02/08/13	Akm Khairuzzaman
LNC	N/A		
Methods Validation	Pending		DPA, St Louis, MO
DMEPA	Proprietary Name Granted	02/12/13	James Schlick
EA	Categorical exclusion granted.	04/02/13	Amit Mitra
Microbiology	Recommend for approval	02/13/13	Bryan Riley

DMEPA: Division of Medication Error Prevention and Analysis; DPA: Division of Pharmaceutical Analysis in St. Louis

The Chemistry Review for NDA 202806

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of Chemistry, Manufacturing and Controls (CMC), this NDA is recommended for 'approval' pending an overall acceptable recommendation from 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

Dabrafenib is a new molecular entity that has no chiral centers and is manufactured as a mesylate salt. (b) (4)

The manufacture of dabrafenib mesylate from starting materials involves (b) (4) Potential and actual impurities (b) (4) were identified. The critical process parameters were identified and the reaction parameters were controlled to properly minimize the formation of these impurities. Four related impurities, (b) (4)

The drug substance is stable under long-term and accelerated stability studies. Under forced degradation study, the drug substance was also found (b) (4) No extraordinary storage precautions are required. A retest period of (b) (4) at the recommended controlled room temperature storage conditions is supported by drug substance stability data.

(2) Drug Product

The drug product section of this NDA was reviewed by Dr. Amit Mitra.

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

The 50 mg Capsules are Dark red capsules imprinted with 'GS TEW' and '50 mg' and they are available in bottles of 120 (NDC 0173-0846-08). Each bottle contains a silica gel desiccant.

The 75 mg Capsules are Dark pink capsule imprinted with 'GS LHF' and '75 mg' available in bottles of 120 (NDC 0173-0847-08). Each bottle contains a silica gel desiccant.

C. Basis for Approvability or Not-Approval Recommendation

- The applicant provided satisfactory information on the manufacturing, control and stability of the drug substance. However, the Office of Compliance has yet to provide an overall acceptable recommendation for the manufacturing and testing sites.
- From the perspective of chemistry, manufacturing and controls, this NDA is recommended for approval, pending an "acceptable" overall recommendation 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/

GAETAN LADOUCEUR
04/10/2013

NALLAPERUM CHIDAMBARAM
04/10/2013
I concur.

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

NDA Number: 202-806	**Supplement Number and Type:**	**Established/Proper Name:** Dabrafenib Capsules
Applicant: GlaxoSmithKline(GSK), LLC	**Letter Date:** 29 July, 2012 (~~Resubmission~~)	**Stamp Date:** 30 July, 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		HMPC capsules issues for Phase 3 was discussed on Dec, 3 2010 *Phase 1 -3 Meeting was held on May 4, 2010 .* *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.Debasis Ghosh. 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 may be needed
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	Yes		By ONDQA QbD Liaison, Dr. Debasis Ghosh . 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.Debasis Ghosh. 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		Capsule. 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
4544	III	Selig Sealing Products, Inc.	Closure Liner	Yes	
1466	III	AmcorPackaging Pharmaceutical & Personal Care, Inc.	HDPE Bottle	Yes	
4837	III	Raxam Closure Systems, Inc	Child Resistant Closure	Yes	
1016	III	Chevron Phillips Chemical Co., LP	HDPE Resin	Yes	
2880	III	Sud-Chemie	Silica Gel Desiccant	Yes	
5828	III	Van Blarcom Closures,Inc.	Child Resistant Closure	Yes	

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

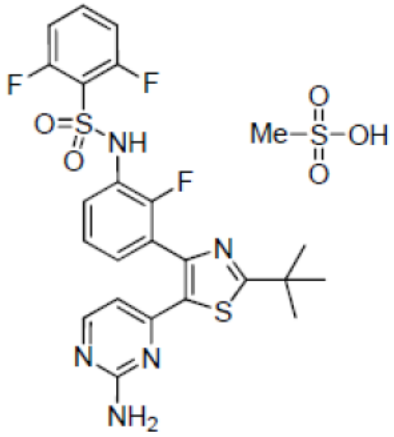
I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	Yes		
33.	Have the immediate container and carton labels been provided?	Yes		

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 (also see below note and 8-30-12 Telecon meeting min). 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:

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation

The drug substance is Dabrafenib mesylate [redacted] (b) (4) with the following chemical structure:



[redacted] (b) (4) The applicant claims that the CQAs of dabrafenib mesylate drug substance have been identified and the resultant specification contains tests for description, identification, dabrafenib mesylate content, drug-related impurities content, residual solvents content, water content, residue on ignition, heavy metals and particle size. Batch analysis data are provided for six production-scale batches of dabrafenib mesylate, which were manufactured according to the proposed commercial route at the commercial site and tested by the proposed commercial methods. All batches were manufactured at the GSK commercial site in Jurong, Singapore. Three of the batches were micronized at [redacted] (b) (4) and the other three batches at [redacted] (b) (4) [redacted]. Twelve months of stability data are presented for three primary stability batches, which were manufactured on commercial scale at the GSK commercial site in Jurong, Singapore, and micronized [redacted] (b) (4) The data seems to be supportive for the chemical and physical stability of drug substance [redacted] (b) (4) [redacted]

Dabrafenib Capsules, 50 mg, are opaque, [redacted] (b) (4) capsules composed of a dark red body and a dark red cap. Capsule shells will be printed with the identifying codes 'GS TEW',

and '50 mg'. Each capsule, intended for oral administration, contains 59.25 mg of dabrafenib mesylate equivalent to 50 mg of dabrafenib free base. Dabrafenib Capsules, 75 mg, are opaque, (b) (4) capsules composed of a dark pink body and a dark pink cap. Capsule shells will be printed with the identifying codes 'GS LHF', and '75 mg'. Each capsule, intended for oral administration, contains 88.88 mg of dabrafenib mesylate equivalent to 75 mg of dabrafenib free base. Dabrafenib Capsules, 50 mg and 75 mg are packed with silica gel desiccant into opaque, white HDPE bottles, and closed with (b) (4), with a (b) (4) induction heat seal liner.

Dabrafenib Capsules are simple immediate release capsule formulations manufactured (b) (4). The Drug Product CQAs of Dabrafenib Capsules, 50 mg and 75 mg are description, identification, content, drug-related impurities content, uniformity of dosage units, and dissolution. Factors influencing Drug Product CQA variability have been established and controls have been defined to ensure that the performance criteria are included in this submission . Attributes and parameters within unit operations of the drug product manufacturing process that influence these drug product Critical Quality Attributes have been discussed and risk assessments conducted to establish their criticality to product performance. The proven acceptable ranges established for the commercial manufacture of the product are well controlled and critical process parameters are within the ranges identified.

Batch analysis data are provided for three production-scale batches of Dabrafenib Capsules, 50 mg, and three production-scale batches of Dabrafenib Capsules, 75 mg, manufactured at each of the commercial sites (GlaxoSmithKline Inc., (b) (4) (b) (4) (b) (4)

Dabrafenib Capsules have been developed using a QbD approach, in line with ICH Q8, Q9, Q10 and other regulatory guidance. Within GlaxoSmithKline (GSK), QbD principals are applied using an internal framework termed 'Design for Manufacture' (DFM). The DFM framework enables identification of the Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) and defines the Control Strategy for the product to assure quality. However, it appears that there are no actual data are submitted in this submission

- Defining acceptable mesylate impurities limits since they are genotoxic impurities
- Total impurities and individual impurity acceptance criteria should be evaluated. It appears that acceptance criteria might need be (b) (4) (also see Tox section).
- It appears that the applicant refers to ICHQ8, 9, 10 and 11 guidances for DOE and 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) if limited stability data from DP manufactured in UK is accepted.
- No test for the microbial limit testing is proposed and this will be a review issues since DP might be (b) (4). (b) (4) Please note that HMPC capsules used for Phase 3 studies was discussed on Dec, 3 2010. It seems that no CMC and ONDQA biopharm isses were discussed regarding HMPC capsule issue. Appropriate dissolution method needs to be reviewed by ONDQA Biopharm team.
- The CMC team review is recommended if this is designated as a priority NDA.

(b) (4)

Liang Zhou *8-30-2012*

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

{ Nallaperum, Chidambaram} *8-30-2012*

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

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/s/

LIANG ZHOU
08/31/2012

NALLAPERUM CHIDAMBARAM
08/31/2012

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