

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203756Orig1s000

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo

NDA 203756, COMETRIQ/Cabozantinib (S)-Malate Capsules, 20 mg and 80 mg

Date: 13-NOV-2012

Background and ONDQA Recommendation:

COMETRIQ Capsules are oral capsules which are manufactured in two dosage strengths: 20 and 80 mg. The recommended daily dose is 140 mg. The proposed indication is treatment of unresectable, locally advanced, or metastatic medullary thyroid cancer.

The Chemistry, Manufacturing and Controls (CMC) section of this original 505(b)(1) NDA submission was received 09-MAR-2011 from Exelixis, Inc. Several solicited CMC amendments were also reviewed during the review clock. The NDA is supported by IND (b) (4) and twelve (12) drug master files (DMFs). An overall acceptable recommendation was received from the Office of Compliance on 23-JUL-2012, and the OPS Microbiology reviewer (Dr. D. Miller) recommended approval from a Microbiology standpoint in her 10-OCT-2012 review.

The drug substance, cabozantinib (S)-malate, (b) (4) that is manufactured (b) (4) the drug substance is tested via appropriate specifications that include testing for appearance, identity, assay and impurities, (b) (4) genotoxic impurities, water content, residual solvent, inorganic impurities, (b) (4) heavy metals and particle size distribution. The justification of the proposed specifications is captured in the Chemistry Review.

The drug product is manufactured (b) (4) (b) (4) Once manufactured, finished capsules are packaged in one of two configurations: blister cards or a high density polyethylene bottle (which contains 60 x 20 mg capsules). All packaging components are adequately supported by information contained in the NDA as well as cross-referenced DMFs (see page 142 of the Chemistry Review for further details on specific packaging schemes).

The comprehensive CMC assessment is captured in the following reviews: Chemistry Review #1 (06-NOV-2012, M. Adams and Dr. L. Hsieh) and the ONDQA Biopharmaceutics Review #1 (29-OCT-2012, Dr. M. Hughes). Both reviews capture the team's recommendation of "Approval" from a CMC standpoint, and according to both reviews, there are no outstanding CMC issues that preclude an approval recommendation.

I concur with the ONDQA team's recommendation of approval for this NDA, and I agree that there are no outstanding CMC issues. As per the 06-NOV-2012 Chemistry Review, the team agrees with the Applicant's proposed expiration dating period (24 months when stored at controlled room temperature); therefore, no additional confirmatory language is needed in the action letter.

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/s/

SARAH P MIKSINSKI
11/14/2012

NDA 203756

Cometriq™ Cabozantinib (S)-Malate capsules (20mg & 80mg)

Exelixis, Inc.

**William M. Adams (drug substance)
Li-Shan Hsieh (drug product)
Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I/Branch II**

**For the Office of Hematology and Oncology Drug Products
Division of Drug Oncology Products II**

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CMC Review Data Sheet

CMC Review Data Sheet

1. **NDA 203756**
2. **REVIEW #1**
3. **REVIEW DATE:** 06 Nov 2012
4. **REVIEWER:** William M. Adams for drug substance
Li-Shan Hsieh, Ph.D. for drug product
5. **PREVIOUS DOCUMENTS:**

<i>Previous Documents</i>		<i>Document Date</i>
IND	(b) (4) - initial submission	10-Jun-2005
IND	(b) (4) - CMC review	12-Jul-2005
IND	(b) (4) - CMC end-of-phase-2 meeting	04-Mar-2012
IND	(b) (4) - End-of phase-2 meeting	06-Mar-2008
IND	(b) (4) - CMC included pre-NDA meeting	20-Dec-2011

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

<i>Submission(s) Reviewed</i>	<i>DARRTS SD Number</i>	<i>Document Date</i>	<i>Stamp Date</i>
CMC Submission	01	08 Mar 2012	09 Mar 2012
Multidiscipline Submission	02	21 May 2012	29 May 2012
Trade name proposal	03	31 May 2012	31 May 2012
IR letter for Biopharm	---	09 Jul 2012	09 Jul 2012
Draft labels	08	20 Jul 2012	20 Jul 2012
Response to IR letter for Biopharm	09	31 Jul 2012	01 Aug 2012
Draft labeling	12	10 Aug 2012	10 Aug 2012
IR letter for Biopharm & DMEPA	---	30 Aug 2012	30 Aug 2012
Revised drug product specification	14	13 Sep 2012	13 Sep 2012
Draft labeling	15	26 Sep 2012	26 Sep 2012
Draft labels and labeling	16	09 Oct 2012	10 Oct 2012
IR letter for CMC – API	---	12 Oct 2012	12 Oct 2012
Drug product stability data	17	15 Oct 2012	16 Oct 2012
Response to IR letter for CMC – API	18	19 Oct 2012	19 Oct 2012
TCon regarding GTI criteria for API	---	23 Oct 2012	23 Oct 2012
Revised API stability protocol	19	26 Oct 2012	26 Oct 2012
IR letter for CMC – DP (GTI criteria)	---	01 Nov 2012	01 Nov 2012
Response to IR letter for CMC - DP	e-mail to RPM	02 Nov 2012	02 Nov 2012

7. **NAME & ADDRESS OF APPLICANT:**

CMC Review Data Sheet

Name: Exelixis, Inc.
Address: 210 East Grand Avenue, South San Francisco, CA 94083
Representative: Kirk Rosemark, Product Manager, RAC, VP, Regulatory Affairs
Telephone: 650-837-7038

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) **Proprietary Name:** Cometriq™
b) **Non-Proprietary Name:** Carbozantinib (S)-malate capsule
c) **Code Name (ONDQA only):** XL184, EXEL-7184, EXEL-02977184, BMS-907351, BMS-907351-01, BMS-907351-02, XL184-1-6
d) **Chem. Type/Submission Priority (ONDQA only):**
- **Chem. Type:** 1
 - **Submission Priority:** S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)**10. PHARMACOL. CATEGORY:** multi-targeted inhibitor of receptor tyrosine kinases (RTKs)**11. DOSAGE FORM:** Hard Gelatin Capsules**12. STRENGTH/POTENCY:** 20-mg and 80-mg as freebase**13. ROUTE OF ADMINISTRATION:** Oral**14. Rx/OTC DISPENSED:** Rx OTC**15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

SPOTS product – Form Completed

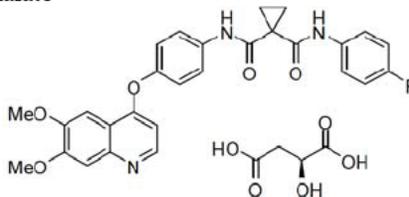
Not a SPOTS product

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

Chemical Name	<i>N</i> -{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}- <i>N'</i> -(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2 <i>S</i>)-hydroxybutanedioate
USAN	Cabozantinib (S)-malate
CAS Number	1140909-48-3
Code Name	XL184, EXEL-7184, EXEL-02977184, BMS-907351, BMS-907351-01, BMS-907351-02, XL184-1-6
Other Names	Butanedioic acid, 2-hydroxy-, (2 <i>S</i>)-, compound with <i>N</i> -[4-[(6,7-dimethoxy-4-quinolinyl)oxy]phenyl]- <i>N'</i> -(4-fluorophenyl)-1,1-cyclopropanedicarboxamide (1:1) Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, L-malate salt

CMC Review Data Sheet

N-[4-(6,7-dimethoxyquinolin-4-yloxy)phenyl]-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2*S*)-hydroxybutanedioate
 XL184 L-malate salt
 Cabozantinib malate



Molecular Formula C₂₈H₂₄FN₃O₅·C₄H₆O₅

Molecular Weight 635.6 Daltons (L-malate salt), 501.5 Daltons (freebase)

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

<i>DMF</i>	<i>TYPE</i>	<i>HOLDER</i>	<i>ITEM</i>	<i>CODE</i> ¹	<i>STATUS</i> ²	<i>DATE</i>	<i>COMMENT</i>
(b) (4)	III			(b) (4)	4		
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	IV			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

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)

³ Include reference to location in most recent CMC review

B. Other Supporting Documents:

<i>DOCUMENT</i>	<i>APPLICATION NUMBER</i>	<i>DESCRIPTION</i>
IND	(b) (4)	Initial IND
IND	113446/SN-021	Expanded Access Study

18. CONSULTS/CMC-RELATED REVIEWS:

CMC Review Data Sheet

CONSULTS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	23-Jul-2012	Office of Compliance
Pharm/Tox	Pending		
Biopharm	Acceptable	29-Oct-2012	Dr. Minerva Hughes
LNC			
Methods Validation	N/A		
DMEPA*			
EA	Acceptable	29-Oct-2012	Dr. Li-Shan Hsieh
Microbiology	Approval	10-Oct-2012	Dr. Denise A Miller

*DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary Section

The CMC Review for NDA 203756

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered Adequate for Chemistry Manufacturing and Control – drug substance and drug product - in that complete and acceptable data and information has been submitted. The CMC review team recommends that the application be Approved.

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)

Drug Substance

Cabozantinib (S)-malate (b) (4)

Structure elucidation studies have established the molecular structure, (b) (4)

The proposed commercial manufacturing process is a (b) (4). The manufacturing process, in-process controls and intermediate specifications are described in sufficient detail. (b) (4)

Adequate specifications for the designated starting materials, (b) (4) reagents, and solvents are provided. (b) (4)

. Manufacture and testing is at a single site in (b) (4) with contract laboratories in (b) (4). All three sites have been found to meet cGMP requirements.

The release specification includes testing for appearance, identity, assay/ordinary impurities, (b) (4) four GTIs, water content, residual solvents, inorganic impurities, (b) (4) heavy metals and particle size distribution. Each method is described in sufficient detail and validated for its intended use. Methods for impurities are sensitive to appropriate levels.

Executive Summary Section

Criteria are justified by batch analysis data and non-clinical studies. Reference standards have been established for drug substance and potential impurities.

Stability information includes forced degradation, heat stress, light stress and long term studies. These studies indicate sensitivity to acid hydrolysis (formation of ordinary impurities) and high heat (formation of GTIs). The proposed post approval stability protocol and commitment are acceptable. The results from the long term studies on commercial lots stored at ICH conditions are sufficient to support storage of bulk drug substance at (b) (4) with a retest period of (b) (4).

Drug Product

COMETRIQ™ (cabozantinib) capsules contain drug equivalent to 20 mg or 80 mg freebase and the following inactive ingredients: silicified microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate, fumed silica, and stearic acid.

Drug product is manufactured by (b) (4). The manufacturing procedure and process controls are described in sufficient detail. The Cabozantinib (XL184) 20-mg capsule is a gray, opaque, (b) (4) two-piece hard gelatin capsule imprinted with “XL184 20 mg” on the capsule body. Capsule fill contains (b) (4). The Cabozantinib 80-mg capsule is a Swedish orange, opaque, (b) (4) two-piece hard gelatin capsule imprinted with “XL184 80 mg” on the capsule body. Capsule fill contains (b) (4). Capsule shell and imprinting ink components are described in sufficient detail.

COMETRIQ™ capsules will be marketed as a blister card or a high density polyethylene bottle with child resistant closure. For the blister cards, each row of capsules represents a daily dose of 60 mg, 100 mg or 140 mg and each card provides a 7-day drug supply. Four cards are packaged into a carton to provide a 28-day supply. The bottle contains sixty 20 mg capsules as a 28-day drug supply.

The quality of COMETRIQ™ capsules has been assessed based on its manufacturing process and process controls; the analytical procedures for identification, purity, strength, and sterility; and stability. Based on the submitted stability data, a 24 months expiry period has been granted with storage at controlled room temperature.

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

20 mg or 80 mg Cometriq™ capsules are to be administered as a 140 mg once daily oral dose taken without food (fasting 2 hours before and 1 hour after dosing) for the treatment of unresectable, locally advanced, or metastatic medullary thyroid cancer (MTC). Dosing is to continue until the patient is no longer clinically benefiting from therapy or there exists an unacceptable toxicity.

C. Basis for Approvability or Not-Approval Recommendation

Executive Summary Section

The requirements of 21 CFR 314.50(d)(1) have been adequately met by the applicant. All drug substance and drug product manufacturing, packaging and control facilities were submitted to EES and found Acceptable.

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

William Adams - reviewer for drug substance
DNDQA I, ONDQA

Li-Shan Hsieh, Ph.D. - reviewer for drug product
DNDQA I, ONDQA

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

Nallaperumal Chidambaram, Ph.D., acting Branch Chief, Branch II
DNDQA I, ONDQA

C. CC Block: *(entered electronically in DARRTS)*

ONDQA/PMQ/J.Martin
ONDQA/CMC Lead/L.Zhou
DOP2/RPM/G.Davis

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/s/

WILLIAM M ADAMS
11/06/2012

LI SHAN HSIEH
11/06/2012

NALLAPERUM CHIDAMBARAM
11/06/2012
I concur

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

NDA Number:
203-756

Supplement Number and Type:

Established/Proper Name:
Cabozantinib

Applicant: Exelixis, Inc.

Letter Date: 29 May, 2012
(Rolling submission for CMC section on 9 March, 2012)

Stamp Date:
29 May, 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		Pre-NDA Meeting on 20 December, 2011 (refer to IND113446 and (b)(4) Meeting min)

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	Yes		
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

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • 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.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

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: <ul style="list-style-type: none"> • 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		

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

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?		No	Dr. Debasis Ghosh
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		No	Dr. Debasis Ghosh

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW 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 Biopharm. See biopharm filing review in DARRTS. Also IR will be issued.
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?			Note that agreed on March 9, 2012 meeting not to submit the stability data until the completion of NDA submission (clinical section) and EES sites for ready inspections).
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		No	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		No	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

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

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

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA Provided
(b) (4)	III		(b) (4)	yes
	III		yes	
	IV		yes	
	III		yes	

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	Yes		Salt /established name needs to be evaluated Therapeutic dose calculations need to be evaluated by teams

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

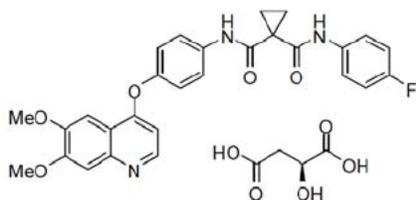
33.	Have the immediate container and carton labels been provided?	Yes		
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PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

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.
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		No	

Note: Cabozantinib, a new molecular entity, is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumor growth and angiogenesis, pathologic bone remodeling, and metastatic progression of cancer. The proposed indication for cabozantinib is for the treatment of patients with progressive, unresectable, locally advanced or metastatic medullary thyroid cancer (MTC).

Chemical structure:



Chemical Name:

N-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-*N'*-(4 fluorophenyl)cyclopropane-1,1-dicarboxamide, (2*S*)-hydroxybutanedioate

Molecular Formula: C₂₈H₂₄FN₃O₅·C₄H₆O₅

Molecular Weight: 635.6 Daltons (L-malate salt), 501.5 Daltons (freebase)

There are several potential concerns as follows:

- The proposed dose name needs to be evaluated (salt vs free base),
- IR letter for the dissolution method needs to be issued (refer to Drs. LiShan Hsieh's draft review/e-mail and Minerva Hughes e-mails)
- Total impurities and individual impurity acceptance criteria for DS should be evaluated .
- Genotoxic Impurity ^{(b) (4)} specification will ne further evaluated by

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

CMC and Pharm/tox team

- All sites were submitted in EES

Liang Zhou

6--27-2012

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

Date

{Janice Browm}

6-27-2012

Name of
CMC Lead
Division of Pre-Marketing Assessment # 1
Office of New Drug Quality Assessment

Date

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
06/28/2012
Rolling Submission for CMC section on March 9, 2012.

JANICE T BROWN
06/28/2012