

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208692Orig1s000

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information**

Memorandum

Date: 04/11/2016

To: Rajesh Venugopal
Regulatory Project Manager
Division of Oncology Products 1 (DOP1)
Office of Hematology and Oncology Products

From: Nazia Fatima, Pharm.D, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: CABOMETYX™ (cabozantinib) tablets, for oral use
NDA 208692

Office of Prescription Drug Promotion Comments on proposed
labeling (PI) and Patient Package Insert (PPI)

Office of Prescription Drug Promotion (OPDP) has reviewed the package insert (PI) and the Patient Package Insert (PPI) for Cabometyx™ (cabozantinib) tablets for oral use as requested in consult from DOP1 dated November 06, 2015.

OPDP's review of the proposed PI and PPI is based on the substantially completed draft labeling titled, "1-4-1-3-cabometyx-draft-redline_4.4.16" sent via electronic mail on April 05, 2016 to OPDP (Nazia Fatima) from DOP1 (Rajesh Venugopal). OPDP comments are provided directly on the marked-up version of the label attached below. Combined OPDP and Division of Medical Policy Programs (DMPP) comments on the proposed PPI were provided under a separate cover and entered in DARRTs on 04/11/16.

If you have any questions please feel free to contact me, Nazia Fatima at 240-402-5041 or at Nazia.Fatima@fda.hhs.gov. Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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/s/

NAZIA FATIMA
04/14/2016

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 208692

Product Name:

CABOMETYX™ (cabozantinib) tablets

PMC Description:

Combine all available PK data from different patient populations and healthy subjects in an integrated population PK model to evaluate the potential impact of tumor types on the PK of cabozantinib.

PMR/PMC Schedule Milestones: Final Report Submission:

06/30/2016

Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Similar steady-state exposures were observed at different doses across patient populations of medullary thyroid cancer (MTC, 140 mg capsules), advanced renal cell carcinoma (RCC, 60 mg Tablets), and castration-resistant prostate cancer (CRPC, 60 mg tablets). This result is unexpected as insignificant difference between capsule and tablet formulations at 140 mg dose. To explore the underlying causes responsible for the similarity in the exposure between different formulations, different doses, and different patient population is important to better understand the drug.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this PMC is to evaluate the potential impact of (b) (4) on the PK of cabozantinib (b) (4) PK data from different patient populations and healthy subjects in an integrated population PK model.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/s/

PENGFEI SONG
04/13/2016

QI LIU
04/13/2016

GEOFFREY S KIM
04/13/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: April 11, 2016

To: Geoffrey Kim, MD
Director
Division of Oncology Products 1 (DOP1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Rowell Medina, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Nazia Fatima, PharmD, MBA, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): CABOMETYX (cabozantinib)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 208692

Applicant: Exelixis, Inc.

1 INTRODUCTION

On October 13, 2015, Exelixis, Inc. submitted for the Agency's review an initial New Drug Application (NDA) 208692 for CABOMETYX (cabozantinib) tablets. The Applicant submitted the final portion of the rolling submission on December 22, 2015. The proposed indication for CABOMETYX (cabozantinib) tablets is for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 1 (DOP1) on November, 6, 2015 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for CABOMETYX (cabozantinib) tablets.

2 MATERIAL REVIEWED

- Draft CABOMETYX (cabozantinib) PPI received on December 22, 2015 and received by DMPP and OPDP on April 5, 2016.
- Draft CABOMETYX (cabozantinib) Prescribing Information (PI) received on December 22, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 5, 2016.
- Approved COMETRIQ (cabozantinib) comparator labeling dated November 29, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

ROWELL MEDINA
04/11/2016

NAZIA FATIMA
04/11/2016

BARBARA A FULLER
04/11/2016

LASHAWN M GRIFFITHS
04/11/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: April 1, 2016
Requesting Office or Division: Division of Oncology Products 1 (DOP1)
Application Type and Number: NDA 208692
Product Name and Strength: Cabometyx (cabozantinib) Tablets, 20 mg, 40 mg, and 60 mg
Submission Date: April 1, 2016
Applicant/Sponsor Name: Exelixis
OSE RCM #: 2015-2316-2
DMEPA Primary Reviewer: Tingting Gao, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

Division of Oncology Products 1 (DOP1) requested that we review the revised container labels for Cabometyx (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations in our previous label and labeling reviews.^{1,2}

2 CONCLUSION

The revised container labels for Cabometyx are acceptable from a medication error perspective. We have no further recommendations at this time.

¹ Gao T. Label and Labeling Review for Cabometyx (NDA 208692). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 MAR 2. 14 p. OSE RCM No.: 2015-2316.

² Gao T. Label and Labeling Memo for Cabometyx (NDA 208692). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 MAR 29. 3 p. OSE RCM No.: 2015-2316-1.

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/s/

TINGTING N GAO
04/04/2016

CHI-MING TU
04/04/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: March 29, 2016
Requesting Office or Division: Division of Oncology Products 1 (DOP1)
Application Type and Number: NDA 208692
Product Name and Strength: Cabometyx (cabozantinib) Tablets, 20 mg, 40 mg, and 60 mg
Submission Date: March 16, 2016
Applicant/Sponsor Name: Exelixis
OSE RCM #: 2015-2316-1
DMEPA Primary Reviewer: Tingting Gao, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMO

Division of Oncology Products 1 (DOP1) requested that we review the revised container labels for Cabometyx (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations in our previous label and labeling review.¹

2 CONCLUSION

The revised container labels are unacceptable from a medication error perspective. If there are no stability or product quality concerns, we recommend to remove the statement “Store in the original package.” to minimize the risk of confusion during dispensing and potential delay in therapy if pharmacy needs to dispense a partial bottle quantity (e.g., cash paying customers, or prescription with quantity of 15 tablets). Pharmacy will need to contact the prescriber to change the prescribed quantity, thus may cause a delay in therapy if the prescriber cannot be

¹ Gao T. Label and Labeling Review for Cabometyx (NDA 208692). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 MAR 2. 14 p. OSE RCM No.: 2015-2316.

reached on the same day. In fact, we have received a post-marketing report where Imbruvica labeling states that the medication must be “dispensed in original package”, and created problems for patients who needed a dose reduction who were forced to purchase an entire bottle rather than partial bottle of the medication.²

Therefore, we recommend removing the statement “Store in the original package.” to minimize the risk of delay in therapy if pharmacy needs to call and clarify the prescribed quantity in case they need to dispense a quantity that is less than the proposed 30-count size.

3 RECOMMENDATIONS FOR EXELIXIS

We recommend the following be implemented prior to approval of this NDA:

A. Container labels

1. Remove the statement “Store in the original package.” Post-marketing surveillance showed confusion during dispensing regarding such statement when the drug product does not need to be dispensed in the original container. We are concerned the statement “Store in the original package” will cause confusion and potential delay in therapy when a partial bottle quantity is prescribed. Since there are no stability or product quality concerns, remove the statement “Store in the original package.”

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² Institute for Safe Medication Practices. Safety briefs: Repackaging of Imbruvica is OK. ISMP Med Saf Alert Acute Care. 2014;19(10):2.

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/s/

TINGTING N GAO
03/29/2016

CHI-MING TU
03/29/2016

Clinical Inspection Summary

Date	March 28, 2016
From	Lauren Iacono-Connors, Reviewer
To	Rajesh Venugopal, Senior Regulatory Health Project Manager Harpreet Singh, Clinical Reviewer Michael Brave, Clinical Reviewer Division of Oncology Products 1
NDA #	208692
Applicant	Exelixis, Inc.
Drug	Carbometyx (Cabozantinib)
NME	No
Therapeutic Classification	Priority
Proposed Indication	(b) (4) for the treatment of advanced renal cell carcinoma (RCC) (b) (4) patients who have (b) (4) prior (b) (4) therapy.
Consultation Request Date	November 6, 2015
Summary Goal Date	April 15, 2016 (revised from May 2, 2016)
Action Goal Date	May 13, 2016
PDUFA Date	June 22, 2016 (revised from June 28, 2016)

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data for Study XL184-308 was submitted to the Agency in support of NDA 208692. Four clinical sites, Dr. Nizar Tannir (Site 1417), Dr. Brian Rini (Site 1361), Dr. Hans Hammers, (Site 1224), Dr. Bernard Escudier (Site 3301), and two CROs (b) (4) of Study XL184-308 were selected for audit.

The primary efficacy endpoint, Progression Free Survival (PFS), was determined by an independent radiology review Vendor (b) (4). The efficacy outcome measures reported in the application were verified with the source records generated at (b) (4) for a sample of clinical sites. There were no significant deficiencies.

There were no significant inspectional findings for clinical investigators Dr. Nizar Tannir, Dr. Brian Rini, Dr. Hans Hammers, , Dr. Bernard Escudier, the CRO (b) (4), and the study sponsor Exelixis (as performed by (b) (4)) of Study XL184-308. The data for Study XL184-308 submitted to the Agency in support of NDA 208692, appear reliable based on available information.

II. BACKGROUND

Exelixis, Inc. seeks approval to market cabozantinib (b) (4) for the treatment of patients with advanced renal cell carcinoma (RCC) who have (b) (4) prior (b) (4) therapy. Study XL184-308, the key study supporting this application, is a Phase III, open-label, randomized, controlled study of cabozantinib (XL184) vs everolimus in subjects with metastatic renal cell carcinoma that has progressed after prior VEGFR tyrosine kinase inhibitor therapy.

Study XL184-308: “A Phase 3, Randomized, Controlled Study of Cabozantinib (XL184) vs Everolimus in Subjects with Metastatic Renal Cell Carcinoma that has Progressed after Prior VEGFR Tyrosine Kinase Inhibitor Therapy.”

Number of subjects: 658 subjects were enrolled

Number of sites: 182

Number of countries where subjects were enrolled: 24

Study Period:

Date of first subject enrolled: August 2013

Data cut-off date: May 22, 2015

Primary efficacy endpoint: Progression-Free Survival, per RECIST 1.1, per independent radiology review (IRR).

Sponsor’s interpretation of primary efficacy outcome: Time to event.

Objectives of Inspections:

- a. Verify primary efficacy endpoint of PFS, as determined by the IRR Vendor (b) (4), for a sample of enrolled subjects.
- b. Assess investigator determined PFS for a sample of enrolled subjects.
- c. Verify secondary efficacy endpoint, Overall Survival (OS), for a sample of enrolled subjects.
- d. Identification, documentation, and reporting of AEs for all enrolled subjects.
- e. General compliance with the investigational plan.

III. RESULTS (by site):

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Date	Final Classification
CI#1: Nizar Tannir, M.D. The University of Texas MD Anderson Cancer Center 1155 Pressler St Duncan Building (CPB) Unit 1374 Houston, TX 77030-3721	Protocol: XL184-308 Site Number: 1417 Number of Subjects: 16	February 1-5, 2016	Pending Interim classification: NAI
CI#2: Brian Rini, M.D. Cleveland Clinic Foundation 9500 Euclid Avenue, R35 Cleveland, OH 44195	Protocol: XL184-308 Site Number: 1361 Number of Subjects: 12	January 12- 19, 2016	NAI
CI#3: Hans Hammers, M.D., Ph.D. 2650 Orleans St CRB I. Room 1M46 Baltimore, MD 21287	Protocol: XL184-308 Site Number: 1224 Number of Subjects: 11	February 2-8, 2016	Pending Interim classification: NAI
CI#4: Bernard Escudier, M.D. Institut Gustave Roussy – Medecine Oncologique 114 rue Edouard Vaillant Villejuif, 94805, France	Protocol: XL184-308 Site Number: 3301 Number of Subjects: 23	February 8- 11, 2016	Pending Interim classification: NAI
CRO: (b) (4) (b) (4)	Protocol: XL184-308 Number of Sites: (b) (4)	(b) (4)	Pending Interim classification: NAI
CRO: (b) (4) [IRR] (b) (4)	Protocol: XL184-308 Number of Subjects: (b) (4)	(b) (4)	Pending Interim classification: NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Nizar Tannir, M.D. (Site 1417)

This inspection was performed as a data audit for NDA #208692. The inspection reviewed the conduct of one clinical study (XL184–308). The site screened 17 subjects and 16 were enrolled and treated. At the time of this inspection, seven subjects had completed the study. Study source documents/records of 17 enrolled subjects were compared to the eCRF and data listings submitted to NDA 208692, focusing on inclusion/exclusion criteria compliance, adverse events, treatment regimens and efficacy endpoint verification. Assessment of study oversight and conduct by Dr. Tannir included adverse event reporting practices, test article accountability, and general protocol compliance.

The inspection found no significant deficiencies. The efficacy endpoint data, PFS as determined by the investigator and OS, was verifiable. There was no evidence of under-reporting of AEs.

The data from Site 1417, associated with Study XL184–308, submitted to the Agency in support of NDA 208692, appear reliable based on available information.

2. Dr. Brian Rini, M.D. (Site 1361)

This inspection was performed as a data audit for NDA #208692. The inspection reviewed the conduct of one clinical study (XL184–308). The site screened 14 subjects and 12 subjects were enrolled. At the time of this inspection, seven subjects were discontinued due to disease progression, one was discontinued due to clinical deterioration, and the remaining four were discontinued due to AEs. Six subjects have died and six are in follow-up. Study source documents/records of all 12 enrolled subjects were compared to the eCRF and data listings submitted to NDA 208692, focusing on inclusion/exclusion criteria compliance, adverse events, treatment regimens, and efficacy endpoint verification. Assessment of study oversight and conduct by Dr. Rini included adverse event reporting practices, test article accountability, and general protocol compliance.

The inspection found no significant deficiencies. The efficacy endpoint data, PFS as determined by the investigator and OS, was verifiable. There was no evidence of under-reporting of AEs.

The data from Site 1361, associated with Study XL184–308, submitted to the Agency in support of NDA 208692, appear reliable.

3. Dr. Hans Hammers, M.D., Ph.D. (Site 1224)

This inspection was performed as a data audit for NDA #208692. The inspection reviewed the conduct of one clinical study (XL184–308). The site screened 14 subjects and 11 were enrolled and treated. Study source documents/records of all 14 screened subjects were compared to the eCRF and data listings submitted to NDA

208692, including primary and secondary efficacy endpoints, adverse events/serious adverse events, discontinuations, and concomitant medications for accuracy of the application data listings. Assessment of study oversight and conduct by Dr. Hammers included adverse event reporting practices, concomitant medications, test article accountability, IRB correspondence, general protocol compliance.

The efficacy endpoint data, PFS as determined by the investigator and OS, was verifiable. There was no evidence of under-reporting of adverse events. The inspection found no significant deficiencies. However, there were several minor protocol compliance observations that were discussed with the site. Specifically, routine safety assessments were not always completed. For example, a Week 1 and Week 47 urinalysis were not done for Subject 3189 and a Week 5 ECG was not done for Subject 3466.

The data for Dr. Hammers' site (1224), associated with Study XL184–308 submitted to the Agency in support of NDA 208692, appear reliable based on available information.

4. CI: Bernard Escudier, M.D. (Site 3301)

This inspection was performed as a data audit for NDA #208692. The inspection reviewed the conduct of one clinical study (XL184–308). The site screened 32 subjects and 24 were enrolled and treated. At the time of this inspection 18 subjects had withdrawn due to disease progression, five subjects completed the study, and one remains on study.

A complete record review was done for all 32 screened subjects. For the enrolled subjects, study source documents/records were compared to the eCRF and data listings submitted to NDA 208692, including primary and secondary efficacy endpoints, adverse events/SAEs, discontinuations, and concomitant medications for accuracy of the application data listings. Assessment of study oversight and conduct by Dr. Escudier included adverse event reporting practices, concomitant medications, test article accountability, Ethics Committee/Sponsor correspondence, and general protocol compliance.

The inspection found no significant deficiencies. The efficacy endpoint data, PFS as determined by the investigator and OS, was verifiable. There was no evidence of under-reporting of AEs.

The data for Dr. Escudier's site (3301), associated with Study XL184–308 submitted to the Agency in support of NDA 208692, appear reliable based on available information.

5. CRO: (b) (4) (Independent Radiology Review Vendor)

This inspection was issued to review the conduct of one clinical study (XL184–308), performed in support of NDA #208692. The inspection focused primarily on assessing the accuracy of the tumor response and disease progression source records (images and interpretation) as it pertains to the contractual obligations of the CRO for

Study XL184–308 per Charter. Subject source documents/records generated by the CRO for (b) (4) randomly selected subjects were compared to the eCRF and data listings submitted to NDA 208692. Assessment of (b) (4) conduct of the Charter-Specified CRO responsibilities included training, education, and qualifications of radiologists, correspondence with clinical sites/sponsor, quality assurance, data collection and management, computer system validation and Independent Review Charter review and adherence.

All reviewed subjects' PFS as determined by the CRO radiologists were verified against the data listings submitted to the application. There were no discrepancies. As of this inspection, there have been (b) (4) subjects' primary radiology endpoints generated by (b) (4). There was no evidence of CRO non-compliance with the Charter.

The data from this CRO, associated with Study XL184–308 submitted to the Agency in support of NDA 208692, appear reliable based on available information.

6. CRO: (b) (4)

This CRO inspection assignment was issued to review the conduct of one clinical study (XL184–308), performed in support of NDA 208692. The inspection focused on the CRO's control, oversight and management of Study XL184–308. (b) (4) was responsible for selecting and maintaining information for all clinical investigators, monitoring and clinical conduct of study XL184-308, record keeping and record retention, and to permit regulatory authorities (USFDA) personnel access to, copy and verify any records and reports related to the clinical investigation. (b) (4) answered data queries (b) (4) had oversight of the DSMB and maintains the Trial Master File. (b) (4) was also responsible for the disposition of unused supply of investigational product. Monitoring records were reviewed from 19 clinical sites. Actions taken by (b) (4) to bring non-compliant clinical sites into compliance were also assessed. All contract agreements and the sponsor responsibility transfer agreement were reviewed as appropriate. Reporting practices for adverse events, and serious adverse events were also reviewed.

(b) (4) maintained adequate oversight over the study. There was no evidence of under-reporting of adverse events/serious adverse events. The primary efficacy endpoint was a derived efficacy outcome measure, PFS, based upon tumor response per RECIST1.1 determined by the IRR, performed by CRO (b) (4). Compliance with the investigational plan appeared to be adequate. Monitoring appeared adequate.

The data from this CRO submitted to the Agency associated with Study XL184–308 submitted to the Agency in support of NDA 208692, appear reliable based on available information.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
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CC:

Central Doc. Rm. NDA #208692
DOP1/Division Director/Geoffrey Kim
DOP1/Clinical Team Leader/Julia Beaver
DOP1/Project Manager/Rajesh Venugopal
DOP1/Medical Officer/Harpreet Singh
DOP1/Medical Officer/Michael Brave
OSI/Office Director (Acting)/David Burrow
OSI/DCCE/ Division Director/ Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Susan D. Thompson
OSI/DCCE/GCP Reviewer/Lauren Iacono-Connors
OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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LAUREN C IACONO-CONNORS
03/28/2016

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03/28/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Pharmacovigilance Memo

Date: March 17, 2016

Reviewer: Afrouz Nayernama, PharmD, Safety Evaluator
Division of Pharmacovigilance II (DPVII)

Team Leader (Acting): Shaily Arora, PharmD
DPVII

Deputy Division Director: S. Christopher Jones, PharmD, MPH, MS
DPVII

Product Name: Cometriq®, Cabometyx® (cabozantinib)

Subject: Drug-drug interaction: Cabozantinib and Warfarin

Application Type/Number: NDA 203756, NDA 208692

Applicant/Sponsor: Exelixis

OSE RCM #: 2016-513

1 INTRODUCTION

This memorandum evaluates cases of drug interaction between cabozantinib and warfarin reported in the FDA Adverse Event Reporting System (FAERS) and the literature. The Division of Pharmacovigilance II (DPVII) identified a literature case report of the drug interaction between cabozantinib and warfarin in a renal cell carcinoma treated patient, during routine FAERS monitoring.¹ We considered this a potential safety signal, as this interaction is not labeled for either drug. The purpose of this memorandum is to evaluate the evidence from the published literature and FAERS to determine if any regulatory actions are required at this time.

1.1 REGULATORY HISTORY

Cabozantinib was approved by FDA on November 29, 2012 under the trade name Cometriq[®] for treatment of patients with progressive, metastatic medullary thyroid cancer (MTC).² Of note, the sponsor, Exelixis is currently seeking a new indication, renal cell carcinoma, for cabozantinib under a new proposed trade name, Cabometyx[®].

1.2 BACKGROUND

Exelixis, submitted a new drug application reference to- (NDA 208692) for cabozantinib for the treatment of advanced renal cell carcinoma in patients who have received (b) (4) prior therapy.³ On February 29, 2016, during one of the multidisciplinary review team's meetings for NDA 208692, DPVII shared the published literature case of the drug-drug interaction (DDI) between cabozantinib and warfarin resulting in International Normalized Ratio (INR) elevation with the Division of Oncology Products 1(DOP1) and discussed the inclusion of this DDI in the cabozantinib product labels. We agreed to complete a follow up review with our regulatory recommendations.

1.3 CLINICAL PHARMACOLOGY²

Cabozantinib inhibits the tyrosine kinase receptors of RET, MET, VEGFR-1&2, KIT, TRKB, FLT-3, AXL, and TIE-2. These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis, and maintenance of the tumor microenvironment.

Cabozantinib is a noncompetitive inhibitor of CYP2C8, a mixed-type inhibitor of both CYP2C9 and CYP2C19, and a weak competitive inhibitor of CYP3A4 in human liver microsomal (HLM) preparations. Cabozantinib is an inducer of CYP1A1 mRNA in human hepatocyte, but not of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 mRNA or isozyme-associated enzyme activities.

1.4 PRODUCT INFORMATION²

The potential drug interaction between cabozantinib and warfarin is not a labeled event with cabozantinib or warfarin.^{2,4} However, the drug interactions between cabozantinib with CYP3A4 inhibitors and inducers are labeled for Cometriq®, as described below.

5 WARNINGS AND PRECAUTIONS

5.10 Drug Interactions

Avoid administration of COMETRIQ with agents that are strong CYP3A4 inducers or inhibitors [see Dosage and Administration (2.1) and Drug Interactions (7.1, 7.2)].

7 DRUG INTERACTIONS

7.1 Effect of CYP3A4 Inhibitors

Administration of a strong CYP3A4 inhibitor, ketoconazole (400 mg daily for 27 days) to healthy subjects increased single-dose plasma cabozantinib exposure (AUC_{0-inf}) by 38%. Avoid taking a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) when taking COMETRIQ [see Dosage and Administration (2.1) and Warnings and Precautions (5.10)].

7.2 Effect of CYP3A4 Inducers

Administration of a strong CYP3A4 inducer, rifampin (600 mg daily for 31 days) to healthy subjects decreased single-dose plasma cabozantinib exposure (AUC_{0-inf}) by 77%. Avoid chronicco-administration of strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, St. John's Wort) with COMETRIQ [see Dosage and Administration (2.1) and Warnings and Precautions (5.10)].

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of Search	February 26, 2016
Time Period of Search	November 29, 2012 [†] - February 26, 2016
Search Type	FBIS- Quick Query
Product Terms	Active ingredient: cabozantinib , cabozantinib s-malate
MedDRA Search Terms:	Drug interaction, Potentiating drug interaction,

Table 1. FAERS Search Strategy*	
Preferred terms (PTs) (version 18.1)	International normalised ratio abnormal, International normalised ratio fluctuation, International normalised ratio increased
* See Appendix A for a description of the FAERS database.	
† US Approval date	

2.2 LITERATURE SEARCH

Table 2. Literature Search Strategy	
Data of search	February 26, 2016
Database	PubMed; Google Scholar
Search Terms	Cabozantinib, Cometriq, warfarin, Coumadin, interaction, drug-drug interaction, CYP3A4, CYP450, inducer, inhibitor, international normalized ratio, protein kinase inhibitors
Years included in search	All

3 RESULTS

3.1 FAERS RESULTS

The FAERS search retrieved 12 reports. After accounting for duplicate reports (n=3) and excluding cases that were not warfarin and cabozantinib interactions (n=7), two cases were included in this case series. One of the two FAERS cases is the index published case report.¹

The narratives of the two cases are described below.

Case#11756236, Expedited Report, USA, Literature¹

A 64-year-old man with metastatic renal cell carcinoma (RCC) started cabozantinib 140 mg orally daily as a third-line of therapy. His prior treatment for RCC included right nephrectomy, and pazopanib for 4 months, but due to disease progression, he underwent palliative radiation therapy. During the postoperative nephrectomy phase, the patient developed pulmonary embolism; he was treated with low-molecular weight heparin and then transitioned to warfarin. The patient was still continuing to take warfarin. Other concomitant medications included zoledronic acid, zolpidem, and ondansetron (as needed). His INR was routinely monitored and prior to initiation of cabozantinib, the INR was stable within the therapeutic range (2.2-3.1) for 3 months. His warfarin dose was 35 to 37.5 mg/week with monthly INR monitoring and clinic visits. The patient's warfarin dose was not adjusted prior to cabozantinib initiation. Approximately two weeks after cabozantinib initiation, he presented for his routine INR monitoring and was found to have an INR of 9.7 with no sign of active bleeding. His warfarin therapy was held and received vitamin K 12.5 mg orally. After 2 days, his INR was 3.4; therefore, warfarin was held for another day. He was instructed to resume warfarin at a lower dose of 27.5 mg per week.

However, after 6 days, he reported nose bleeds and was found to have an INR of 18. The warfarin was held and he was given 5 mg vitamin K; however, after one day, a repeat INR did not show any changes. He was given additional dose of vitamin K and also 4 units of fresh frozen plasma. At this time, cabozantinib was also discontinued. His INR decreased to 2 within 7 days, following these interventions. He was restarted on warfarin at the previously stable dose of 37.5 mg weekly. After two weeks of cabozantinib therapy, he experienced other adverse events including mouth sensitivity, nausea, anorexia, and acneiform skin rash, fatigue, and elevated total bilirubin (3.1 mg/dl); his liver enzymes prior to cabozantinib were normal. His total bilirubin returned to a normal level, two weeks after discontinuation of cabozantinib. The patient did not receive any further therapy for RCC and was referred for home hospice care.

The author suggested that modulation of cytochrome P (CYP) 450 kinetics likely represents the most significant contribution to this interaction. According to cabozantinib product information, cabozantinib is a mixed inhibitor of CYP2C9 and CYP2C19, a noncompetitive inhibitor of CYP2C8, and a minor competitive inhibitor of CYP3A4. These pharmacokinetic effects likely delayed the clearance of warfarin, as warfarin is dependent on CYP2C9 for hepatic metabolism, and cabozantinib is an inhibitor of that enzyme. This could have resulted in excessive inactivation of clotting factors and a subsequent dramatic increase in the INR. There was no suspected drug interaction between warfarin and patient's other concomitant medications. Of note, during phase 1 clinical trial of cabozantinib for RCC, the co-administration of warfarin was not allowed.⁵

***Reviewer's comments:** Based on the temporal relationship, lack of other apparent confounding factors, and the pharmacokinetic profiles of warfarin and cabozantinib, the drug-drug interaction between these two agents resulting in an INR elevation is plausible.*

Case#9186145, Expedited Report, USA

A 52-year-old male with metastatic thyroid cancer started cabozantinib 140 mg orally daily. His past medical history was not reported; the concomitant medications included amlodipine, calcium gluconate, magnesium oxide, levothyroxine, and warfarin. Approximately a month after initiation of cabozantinib, he developed "stroke-like symptoms" and was hospitalized. The MRI of his brain did not show any evidence of recent stroke; however, it showed that he may have had mini-strokes in the past. He was diagnosed with hypertension and elevation of INR (INR>10, no reference range provided). He also experienced diarrhea and gait disturbance. Of note, patient's INR was normal prior to this event and was checked regularly. His blood pressure medication dose was increased to control his blood pressure and he received "plasma infusion to bring his INR back down." The action taken with warfarin and its dose was not reported. At the time of discharge from the hospital, his blood pressure was "normal" and his INR levels "had improved." He was scheduled to check his INR on a weekly basis.

***Reviewer's Comments:** Based on the temporal relationship and no other apparent confounding factors, the drug interaction between cabozantinib and warfarin resulting in INR elevation is plausible.*

3.2 LITERATURE RESULTS

Our literature search did not identify any further relevant cases beyond the one also reported to FAERS.

4 REVIEWER'S COMMENTS

A hands-on review of the drug interaction cases between cabozantinib and warfarin from the FAERS and the literature suggests an interaction between these two drugs based on temporal relationship, positive dechallenge, and biologic plausibility from pharmacokinetic profiles. The risk of bleeding may increase with the concomitant use of cabozantinib and warfarin because of the potential pharmacokinetic interaction (e.g. CYP enzymes and isoenzymes inhibition) between these two agents. Cabozantinib is a mixed inhibitor of CYP2C9 and a weak competitive inhibitor of CYP3A4;² therefore, it has the potential to increase the warfarin effect by inhibiting warfarin metabolism, as warfarin is dependent on CYP2C9 for hepatic clearance. Of note, the potential DDI between cabozantinib and selected other CYP enzymes and isoenzymes inhibitors and inducers are labeled events. However, this potential DDI between cabozantinib and warfarin is unlabeled. Furthermore, serious hemorrhagic events are currently labeled under *Boxed Warnings* and *Warning and Precautions* for cabozantinib (NDA203756, Cometriq®), independent of potential drug interaction with warfarin.

It is noteworthy that a DDI between warfarin and another oral antineoplastic agent, capecitabine, has been described under *Boxed Warnings*, *Warnings and Precautions*, and *Drug Interactions* sections. In a drug interaction study of capecitabine with single-dose warfarin administration, there was a significant increase in the mean AUC of S-warfarin.⁶ The maximum observed INR value increased by 91%. The mechanism of this interaction is also presumed to be inhibition of the CYP2C9 by capecitabine and/or its metabolites.⁶

DPV consulted the FDA 2011 Guidance for Industry for placement of safety information in drug labeling. Information that is placed in the Warnings and Precautions section should describe a serious or otherwise clinically significant event, with reasonable evidence to support a causal relationship to include the extent to which the adverse event is consistent with the pharmacology of the drug, temporal association between drug and the event, existence of dechallenge and rechallenge experiences, whether the adverse event is known to be caused by related drugs, and whether an event can be prevented or mitigated because it has implications for prescribing decisions or for patient management (e.g. need for monitoring to assess safety).⁷

Given the risk of serious hemorrhagic events, we consider this purported DDI to be clinically meaningful. Additionally, CYP2C9 is a common metabolic pathway for both drugs that make this drug interaction plausible. Drug interactions are manageable events with dose modifications, or a change in drug therapy; therefore this new information would be useful to add to labeling as it would have implications for patient management. Moreover, DPV concludes that the concomitant use of warfarin and cabozantinib can result in a significant increase in INR, and

potentially an elevated risk of serious bleeding. Considering serious hemorrhagic events are independently associated with cabozantinib exposure, we recommend labeling revisions to include this potential DDI information in both the cabozantinib and warfarin labels.

5 RECOMMENDATIONS:

DPVII recommends the following:

- Consider consulting the Office of Clinical Pharmacology to better characterize the mechanism and describe this potential interaction, to include instructions for dosage adjustment for warfarin and/or cabozantinib under the *Dosage Administrations* section of cabozantinib product labels, consistent with other drug interactions with cabozantinib.
- Consider inclusion of the purported cabozantinib-warfarin interaction under the *Boxed Warnings, Warnings and Precautions, and Drug Interactions* sections of both cabozantinib (NDA 203756 and NDA 208692) product labels. This would be consistent with the current placement of similar information in capecitabine labeling.⁶
- Consider including the following language under hemorrhagic events under *Warnings and Precautions* and/or *Drug Interactions* sections:
The risk of bleeding may increase with the concomitant use of warfarin attributed to cabozantinib mediated inhibition of CYP2C9 and CYP3A4, which inhibit warfarin metabolism, elevate the INR and increase the risk of clinically significant bleeding. Consider using an alternative anticoagulant.
- Disseminate the information regarding the potential interaction between cabozantinib and warfarin with the Division of Hematology Products (DHP) in order to include cabozantinib under the *Drug Interactions* section of warfarin products labels.
- Consider issuance of an information request (IR) to the sponsor of cabozantinib, Exelixis, regarding the data for the concomitant use of warfarin or other anticoagulants use with cabozantinib in order to better characterize this potential safety issue and determine appropriate dosage adjustment

6 APPENDICES

6.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7 REFERENCES

1. Foxx-Lupo WT, Sing S, Alwan L, et al. A drug interaction between cabozantinib and warfarin in a patient with renal cell carcinoma. *Clinical Genitourinary cancer*. February 2016; 14 (1):e119-121.
2. Cometriq® (cabozantinib) Full Prescribing Information. Exelixis, INC. November 29, 2012.
3. Exelixis, cabozantinib sponsor, NDA 208692 application submitted October 12, 2015. Accessed at DARRTS
<http://darrts.fda.gov:9602/darrts/viewEDR.do?suppDocId=9665329>
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6. Xeloda® (capecitabine) Full Prescribing Information. Genentech Inc. March 19, 2015.
7. FDA-CDER Guidance Documents: Guidance for Industry Warnings and Precautions, Contraindications, and Boxed Warning Sections of labeling for Human Prescription Drug and Biologic Products- Content and Format. October 2011. Accessed at
<http://inside.fda.gov:9003/CDER/OfficeofSurveillanceandEpidemiology/ucm309920.htm>

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/s/

AFROUZ R NAYERNAMA
03/17/2016

SHAILY ARORA
03/17/2016

STEVEN C JONES
03/17/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: March 2, 2016
Requesting Office or Division: Division of Oncology Products 1 (DOP1)
Application Type and Number: NDA 208692
Product Name and Strength: Cabometyx (cabozantinib) Tablets, 20 mg, 40 mg, and 60 mg
Product Type: Single ingredient product
Rx or OTC: Rx
Applicant/Sponsor Name: Exelixis
Submission Date: December 22, 2015 and February 11, 2016
OSE RCM #: 2015-2316
DMEPA Primary Reviewer: Tingting Gao, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

Exelixis Pharmaceuticals submitted container labels for Cabometyx (cabozantinib) tablets on December 22, 2015. The Division of Oncology Products 1 (DOP1) requested that we review the submitted container labels and prescribing information for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We evaluate the proposed container labels and determine that the container labels can be improved to clarify important information (e.g. directions to take Cabometyx) and recommend adding sufficient white space between paragraphs on the side panel to improve readability. Additionally, we noted that the middle digits of the National Drug Code (NDC) numbers are in sequential order (e.g., -023-, -024-, -025-) while the labeler code (42388-) and the package code (-26) remains the same for all three strengths. Our post-marketing experience indicates that similar NDC product code (middle 3 digits) has led to selecting and dispensing of the wrong strength since these middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Assignment of sequential numbers is not an effective differentiating feature. Therefore we recommend changing the middle digits to non-sequential numbers or increasing the prominence of the middle digits by increasing the font size and put them in bold type (e.g., XXXXX-**XXX**-XX).

Since cabozantinib is currently marketed as capsules under the proprietary name Cometriq by the same Applicant Exelixis, we compared the proposed Cabometyx container labels to the

current marketed Cometriq container labels and carton labeling and determined that there are sufficient differentiation between the proposed Cabometyx container labels and the current marketed Cometriq container labels and carton labeling.

We evaluated the proposed prescribing information and recommend to consider adding the statement “Do not substitute CABOMETYX tablets with COMETRIQ capsules.” in the Dosage and Administration section in the Highlights of the PI to minimize the risk of wrong drug and wrong strength errors. Additionally, we also recommend relocating the statement (b) (4) (b) (4) (b) (4) to Section 2 Dosage and Administration. Lastly, we recommend avoid using the word (b) (4) and recommend revise this statement to state (b) (4) (b) (4) (b) (4)

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container labels and PI labeling for Cabometyx may be improved to promote the safe use of the product as described in Section 4.1 and Section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

1. Section 2 Dosage and Administration, Highlights of PI
 - a. Consider adding the statement “Do not substitute CABOMETYX tablets with COMETRIQ capsules.” to minimize the risk of wrong drug and wrong strength errors.
2. Section 3 Dosage Forms and Strengths, Full PI
 - a. Relocate the statement (b) (4) (b) (4) (b) (4) to Section 2 Dosage and Administration. Additionally, we recommend the Review Team to avoid using the word (b) (4) and consider revising this statement to state (b) (4) (b) (4)

4.2 RECOMMENDATIONS FOR EXELIXIS

We recommend the following be implemented prior to approval of this NDA:

1. Container labels
 - a. Assigning National Drug Codes (NDC) with sequential drug product codes (middle digits) for different strengths of the same drug product do not adequately

distinguish the products, and has led to selecting and dispensing of the wrong strength. To better differentiate the NDC numbers, we recommend changing the product codes (middle digits) so that they are not sequential. If these numbers cannot be revised, increase the prominence of the middle digits by increasing their font size in comparison to the remaining digits or putting them in bold type.

For example, XXXXX-**XXX**-XX.¹

- b. On the side panel, revise the order of the statements so direction on the action item appears first such that it reads “Take once each day on an empty stomach. Cabometyx should not be taken with food. Do not eat...” Additionally, we recommend bolding the statement “Take once each day on an empty stomach.” to improve readability.
- c. Remove the statement “store in the original package” on the container labels if there are no stability or product quality concerns that require the tablets be dispensed in the original package to the patients.
- d. If possible, ensure there is sufficient white space between the paragraphs on the side panel to improve readability. This may be achieved by removing the statement “store in the original package”.
- e. Consider adding the statement “Swallow CABOMETYX tablets whole. Do not crush CABOMETYX tablets.” on the side panel if space permits.

¹ Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Cabometyx that Exelixis submitted on December 22, 2015. Since cabozantinib is currently marketed as capsules under the proprietary name Cometriq by the same Applicant Exelixis, we provided the product information for Cometriq for comparison.

Table 2. Relevant Product Information for Cabometyx and Cometriq		
Product Name	Cabometyx (NDA 208692)	Cometriq (NDA 203756)
Initial Approval Date	N/A	November 29, 2012
Active Ingredient	Cabozantinib	Cabozantinib
Indication	advanced renal cell carcinoma (RCC) in patients who have received (b) (4) prior therapy	progressive, metastatic medullary thyroid cancer
Route of Administration	Oral	Oral
Dosage Form	Tablet	Capsule
Strength	20 mg, 40 mg, and 60 mg	20 mg, 80 mg
Dose and Frequency	60 mg once daily (b) (4) Upon resolution/improvement (i.e., return to baseline or resolution to Grade 1) of an adverse reaction related to CABOMETYX, reduce the dose as follows: If previously receiving 60 mg daily dose, resume treatment at 40 mg daily If previously receiving 40 mg daily dose, resume treatment at 20 mg daily If previously receiving 20 mg daily dose, resume at 20 mg if tolerated, otherwise, discontinue CABOMETYX	140 mg once daily (one 80-mg and three 20-mg capsules) Upon resolution/improvement of the adverse reaction (i.e., return to baseline or resolution to Grade 1), reduce the dose as follows: If previously receiving 140 mg daily dose, resume treatment at 100 mg daily (one 80-mg and one 20-mg capsule) If previously receiving 100 mg daily dose, resume treatment at 60 mg daily (three 20-mg capsules) If previously receiving 60 mg daily dose, resume at 60 mg if tolerated, otherwise, discontinue COMETRIQ

Table 2. Relevant Product Information for Cabometyx and Cometriq		
Product Name	Cabometyx (NDA 208692)	Cometriq (NDA 203756)
How Supplied	bottles containing 30 tablets of one strength: 20-mg, 40-mg, or 60-mg	<p>140 mg daily-dose carton containing four 140 mg daily-dose blister cards (each blister card contains seven 80-mg and twenty-one 20-mg capsules)</p> <p>100 mg daily-dose carton containing four 100 mg daily-dose blister cards (each blister card contains seven 80-mg and seven 20-mg capsules)</p> <p>60 mg daily-dose carton containing four 60 mg daily-dose blister cards (each blister card contains twenty-one 20-mg capsules)</p> <p>Bottle containing sixty 20-mg capsules</p>
Storage	20°C to 25°C (68°F to 77°F)	20°C to 25°C (68°F to 77°F)
Container Closure	HDPE bottles	Blister card Bottle

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03/02/2016

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RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208692		Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Cabometyx Established/Proper Name: Cabozantinib Dosage Form: Tablet Strengths: 20 mg, 40 mg, 60 mg		
Applicant: Exelixis, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: December 22, 2015 Date of Receipt: December 22, 2015 Date clock started after UN: N/A		
PDUFA Goal Date: June 22, 2016		Action Goal Date (if different): May 13, 2016
Filing Date: February 19, 2016		Date of Filing Meeting: January 19, 2016
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input checked="" type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): For the treatment of advanced renal cell carcinoma (RCC) ^(b) ₍₄₎ patients who have received ^(b) ₍₄₎ prior therapy		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> • <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> • <i>The product is a Qualified Infectious Disease Product (QIDP)</i> • <i>A Tropical Disease Priority Review Voucher was submitted</i> • <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	

<input checked="" type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): 72596

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>	N/A	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:							
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 				<input type="checkbox"/>	<input type="checkbox"/>	N/A	
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. 				<input type="checkbox"/>	<input type="checkbox"/>	N/A	
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>				<input type="checkbox"/>	<input type="checkbox"/>	N/A	
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p>				<input type="checkbox"/>	<input type="checkbox"/>	N/A	
If yes , please list below:							
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration				
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>							
Exclusivity	YES	NO	NA	Comment			
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Not for same indication, but active moiety has orphan designation for the treatment of follicular, medullary and anaplastic thyroid carcinoma and metastatic or locally advanced papillary thyroid cancer.			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>				

<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>				
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes, # years requested: 3 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL)	<input checked="" type="checkbox"/> All electronic	<input type="checkbox"/> Mixed (paper/electronic)	
	<input checked="" type="checkbox"/> CTD	<input type="checkbox"/> Non-CTD	<input type="checkbox"/> Mixed (CTD/non-CTD)	
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment

If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

(3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment

<u>PREA</u>				
Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Has a review of the available pregnancy and lactation data been included?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Sent on 12.28.15
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Sent on 12.28.15
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL)			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

	<input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): January 17, 2013 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): August 19, 2015 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): April 21, 2008, July 30, 2009, June 23, 2011, September 12, 2011 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 19, 2016

BACKGROUND: NDA 208692 for Cabometyx (cabozantinib) is for the treatment of advanced renal cell carcinoma (RCC) (b)(4) patients who have received (b)(4) prior therapy. The rolling submission was initiated with Seq 0000, submitted on October 13, 2015, which included the Nonclinical and Quality modules. Final clinical datasets for the pivotal phase 3 RCC study XL184-308 were provided under Seq 0003. Seq 0006 provided the Module 5 clinical study reports for all studies aside from Study XL184-308. The final portion of the rolling submission was submitted on December 22, 2015, to begin the review timeline for the Division.

Cabometyx is a kinase inhibitor indicated for the treatment of advanced renal cell carcinoma (RCC) (b)(4) patients who have received (b)(4) prior therapy.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Rajesh Venugopal	Y
	CPMS/TL:	Christy Cottrell	Y
Cross-Discipline Team Leader (CDTL)	Julia Beaver		Y
Division Director/Deputy	Geoffrey Kim/Anna Ibrahim		Y/Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Michael Brave Harpreet Singh	Y/Y
	TL:	Julia Beaver	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		N/A
	TL:		N/A
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		N/A
	TL:		N/A
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		N/A
	TL:		N/A

Clinical Pharmacology	Reviewer:	Pengfei Song	Y
	TL:	Qi Liu	N
• Genomics	Reviewer:		N/A
• Pharmacometrics	Reviewer:	Chao Liu	
Biostatistics	Reviewer:	Joyce Cheng	Y
	TL:	Shenghui Tang	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Eias Zahalka	Y
	TL:	Todd Palmby	Y
Statistics (carcinogenicity)	Reviewer:	Feng Zhou	N
	TL:	Karl Lin	N
Product Quality (CMC) Review Team:	ATL:	Xiao-Hong Chen	Y
	RBPM:	Rabiya Laiq	Y
• Drug Substance	Reviewer:	Xing Wang	Y
• Drug Product	Reviewer:	Xing Wang	Y
• Process	Reviewer:	Ying Zhang	Y
• Microbiology	Reviewer:		N/A
• Facility	Reviewer:	Laura Fontan	Y
• Biopharmaceutics	Reviewer:	Fang Wu	Y
• Immunogenicity	Reviewer:		N/A
• Labeling (BLAs only)	Reviewer:		N/A
• Other (e.g., Branch Chiefs, EA Reviewer)		Anamitro Banerjee, CMC Branch Chief	Y
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Rowe Medina	
	TL:	Barbra Fuller	
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Nazia Fatima	N
	TL:	Jessica Derenick Clerk	N
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Tingting Gao	Y
	TL:	Alice (Chi-Ming) Tu	Y
OSE/DRISK (REMS)	Reviewer:	Carolyn Yancey	Y
	TL:	Naomi Redd	N

OC/OSI/DSC/PMSB (REMS)	Reviewer:		N/A
	TL:		N/A
Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connor	N
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:		N/A
	TL:		N/A
Other reviewers/disciplines			
<ul style="list-style-type: none"> Discipline <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p>	Reviewer:		N/A
	TL:		N/A
Other attendees			N/A
			N/A
			N/A
		*For additional lines, right click here and select "insert rows below"	N/A

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues: <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments 	<input checked="" type="checkbox"/> Not Applicable

List comments:	<input checked="" type="checkbox"/> No comments
CLINICAL Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
CONTROLLED SUBSTANCE STAFF <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>New Molecular Entity (NDAs only)</u></p> <ul style="list-style-type: none"> Is the product an NME? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Geoffrey Kim, MD	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): March 21, 2016	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTION ITEMS	
	How many labeling meetings – 6 +1 Team meetings- 1/February 29, 2016 Will this have a REMS? No #of REMS Meeting – None Wrap-up meeting needed? - Scheduled for April 14, 2016
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter

<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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

/s/

RAJESH VENUGOPAL
02/10/2016

CHRISTY L COTTRELL
02/12/2016

REGULATORY PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208692

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Cabometyx (cabozantinib) Tablets, 20 mg, 40 mg, and 60 mg

Applicant: Exelixis, Inc.

Receipt Date: December 22, 2015

Goal Date: June 22, 2016

1. Regulatory History and Applicant's Main Proposals

NDA 208692 for cabozantinib is indicated for the treatment of advanced renal cell carcinoma (RCC) ^(b)₍₄₎ patients who have received ^(b)₍₄₎ prior therapy. The first piece of the rolling NDA was submitted under Seq 0000 on October 13, 2015, which included the Nonclinical and Quality modules. Final clinical datasets for the pivotal phase 3 RCC study XL184-308 were provided under Seq 0003. Seq 0006 provided the Module 5 clinical study reports for all studies other than Study XL184-308. The final portion of the rolling submission was submitted on December 22, 2015, which began the review clock.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. **Instructions to complete this item:** If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *Reference is not provided for INDICATIONS AND USAGE.*

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required

Selected Requirements of Prescribing Information

• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- NO** 10. Product title must be **bolded**.

Comment: *Product title not bolded.*

Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: *Four digit year not included.*

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the

Selected Requirements of Prescribing Information

BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- YES** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Adverse Reactions in Highlights

Selected Requirements of Prescribing Information

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

- NO** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015** ”).

Comment: *Revision date must be added.*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

***Comment:** For Section 8, the subsections are titled as 8.1 Pregnancy, 8.2 Nursing Mothers, 8.3 Pediatric Use, 8.4 Geriatric Use, 8.5 Females and Males of Reproductive Potential, 8.6 Hepatic Impairment, 8.7 Renal Impairment*

- NO** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed

Selected Requirements of Prescribing Information

within brackets. For example, “[see Warnings and Precautions (5.2)].”

Comment: *The Pharmacokinetics subsection 12.3 is directly referenced in sections 3, 8.6, and 8.7. The cross-reference should be to CLINICAL PHARMACOLOGY (12.3).*

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Selected Requirements of Prescribing Information

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- NO** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment: *None of the above mentioned verbatim statements are included.*

- YES** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

RAJESH VENUGOPAL
01/13/2016

CHRISTY L COTTRELL
02/05/2016