CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203756Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203756

NDA APPROVAL

Exelixis, Inc.
Attention: Lisa Sauer
Director, Regulatory Affairs
210 East Grand Avenue
South San Francisco, CA 94083

Dear Ms. Sauer:

Please refer to your New Drug Application (NDA) dated May 21, 2012, received May 29, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cometriq (cabozantinib) capsules, 20 mg and 80 mg.

We acknowledge receipt of your amendments dated May 31, 2012; June 18, 2012; June 29, 2012; July 2, 2012; July 13, 2012; July 20, 2012; July 31, 2012; August 2, 2012; August 6, 2012; August 7, 2012; August 10, 2012; August 28, 2012; September 13, 2012; September 26, 2012; October 9, 2012; October 15, 2012; October 19, 2012; October 26, 2012; November 2, 2012; November 6, 2012; November 20, 2012; November 27, 2012; November 28, 2012; and November 29, 2012.

This new drug application provides for the use of Cometriq (cabozantinib) capsules, for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted on November 27, 2012, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 203756**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Cometriq (cabozantinib) was not referred to an FDA advisory committee because the clinical study design was acceptable; the application did not raise significant safety or efficacy issues that were unexpected for a drug indicated for the treatment of metastatic medullary thyroid cancer; and there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected, serious risk of carcinogenicity and teratogenicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(1) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1970-1 A rodent carcinogenicity study in the mouse designed according to "FDA Guidance for Industry-Carcinogenicity Study Protocol Submissions". Submit the carcinogenicity protocol for Special Protocol Assessment prior to initiating the study.

The timetable you submitted on November 27, 2012, states that you will conduct this study according to the following schedule:

SPA Submission:	June 2013
Final Protocol Submission:	June 2013
Study Completion:	October 2014
Final Report Submission:	October 2015

1970-2 A rodent carcinogenicity study in the rat designed according to "FDA Guidance for Industry-Carcinogenicity Study Protocol Submissions". Submit the carcinogenicity protocol for Special Protocol Assessment prior to initiating the study.

The timetable you submitted on November 27, 2012, states that you will conduct this study according to the following schedule:

SPA Submission:	April 2013
Final Protocol Submission:	April 2013
Study Completion:	October 2015
Final Report Submission:	October 2016

1970-3 A pre- and post-natal reproductive toxicology study designed according to "ICH Guidance for Industry S5a: Detection of Toxicity to Reproduction for Medicinal Products."

The timetable you submitted on November 27, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	June 2013
Study Completion:	April 2014
Final Report Submission:	October 2014

1970-4 An *in vitro* mutagenicity assay of the M4 metabolite (monohydroxy sulfate).

The timetable you submitted on November 27, 2012, states that you will conduct this study according to the following schedule:

Study Completion:	August 2013
Final Report Submission:	December 2013

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of excessive toxicity at the studied dose, to identify an unexpected serious risk of toxicity in patients with hepatic impairment, to assess a signal of potential toxicity from altered GI absorption, and to identify an unexpected, serious risk of an adverse effect on overall survival.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1970-5 A randomized dose-comparison trial in patients with progressive metastatic medullary thyroid cancer comparing the safety and activity of oral cabozantinib 140 mg daily to a biologically active and potentially safer lower daily cabozantinib dose. The trial will be designed to test non-inferiority of the lower dose to the approved dose for effect on progression-free survival effect and to assess the comparative safety of the two doses.

Safety assessments will include evaluation for all labeled adverse reactions and the analysis plan will provide comparisons of the incidence and severity of the following adverse reactions of cabozantinib: hemorrhage, gastrointestinal and non-gastrointestinal perforations and fistulas, hypertension, diarrhea, oral mucositis/stomatitis, and palmar-plantar erythrodysesthia (PPE) syndrome.

The timetable you submitted on November 27, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	June 2013
Trial Completion:	September 2017
Final Report Submission:	March 2018

1970-6 A clinical trial designed according to "FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function–Study Design, Data Analysis and Impact on Dosing and Labeling". The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant pharmacokinetic paramaters for cabozantinib. A data analysis plan must be included in the protocol. The number of patients enrolled in each of the hepatic function cohorts should be sufficient to reliably detect exposure differences. The trial results should allow for a determination on dosage adjustment recommendations in the label.

The timetable you submitted on November 27, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	December 2012
Trial Completion:	December 2014
Final Report Submission:	June 2015

1970-7 A drug-drug interaction clinical trial to evaluate if gastric pH elevating agents alter the bioavailability of cabozantinib. The trial may be conducted in a gated manner, first evaluating the effect of a proton pump inhibitor (PPI) on the single-dose exposure of cabozantinib. In the event that concomitant administration of a PPI has a large effect on cabozantinib exposure following single-dose administration, H2 antagonist and an antacid will be subsequently evaluated. The number of subjects enrolled in the trial should be sufficient to detect exposure differences. The trial results should allow for a determination on how to dose cabozantinib with regard to concomitant gastric pH elevating agents.

The timetable you submitted on November 27, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	July 2013
Trial Completion:	March 2014
Final Report Submission:	July 2014

Submit the protocols to your IND 113446, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o)

on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

1970-8 Submit the results of the protocol-specified final analysis of overall survival, along with datasets and analysis programs, from Protocol XL184-301.

The timetable you submitted on November 27, 2012, states that you will conduct this trial according to the following schedule:

Trial Completion:	June 2014
Final Report Submission:	December 2014

Submit clinical protocols to your IND 113446 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Gina Davis, Regulatory Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling

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

/s/

GINA M DAVIS
11/29/2012

RICHARD PAZDUR
11/29/2012