CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203756Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	November 20, 2012
From	Patricia Keegan
Subject	Division Director Summary Review
NDA #	NDA 203756
Applicant Name	Exelixis Inc.
Date of Submission	May 21, 2012 (receipt date May 29, 2012)
PDUFA Goal Date	November 29, 2012
Proprietary Name / Established (USAN) Name	COMETRIQ cabozantinib
Dosage Forms / Strength	COMETRIQ 20-mg gelatin capsules; grey capsules with "XL184 20mg" printed in black on the capsule COMETRIQ 80-mg gelatin capsules: Swedish orange with "XL184 80mg" printed in black on the capsule
Proposed Indication(s)	COMETRIQ is indicated for the treatment of patients with progressive, unresectable locally advanced or metastatic medullary thyroid cancer (MTC)
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Gina Davis
Medical Officer Review	Ruthann Giusti
Statistical Review	Yuan-Li Shen
Pharmacology Toxicology Review	Margaret Brower
CMC Review	Minerva Hughes, William M. Adams, Li-Shan Hsieh
Microbiology Review	Denise Miller
Clinical Pharmacology Review	Jun Yang
OPDP	Carole Broadnax & Karen Munoz-Nero
OMP/DMPP Review	Karen Dowdy
DMHS Review	Jeanine Best
OSI	Roy Blay
CDTL Review	Suzanne Demko
OSE/DMEPA	James Schlick
OSE/DRISK	Joyce Weaver
QT/IRT Consult	Satjit Brar

OND=Office of New Drugs
OMP=Office Medical Policy
DMPP=Division of Medical Policy Program
OPDP= Office of Prescription Drug Promotion
PMHS= Pediatric and Maternal Health Staff
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

Cabozantinib is a small molecule inhibitor of multiple receptor-based tyrosine kinases, including RET, MET, and VEGFR2. The clinical development program of cabozantinib in medullary thyroid cancer (MTC) is as a targeted therapy, based on the known correlation between mutation in the *RET* gene and both the hereditary and sporadic forms of MTC. Cabozantinib has the same mechanism of action (inhibition of RET tyrosine kinase) as that of another drug, vandetinib, which was approved for the treatment of metastatic medullary thyroid cancer in 2011, based on a similarly designed trial and endpoints (progression-free survival and durable objective response rate) as that provided in the NDA for cabozantinib.

The NDA is supported by a single, well-conducted, placebo-controlled, randomized (2:1), multi-national trial, Protocol XL184-301, which enrolled 330 patients with metastatic medullary thyroid cancer. Assessment for *RET* mutation was not a requirement of the protocol but was assessed retrospectively in approximately 70% of patients with "research-use only" assays. Protocol XL184-301 demonstrated that treatment with cabozantinib results in a statistically significant and clinically important improvement in progression free survival [HR 0.28 (95% CI: 0.19, 0.40); $p<0.0001$], with an estimated median PFS of 11.2 months for cabozantinib treatment as compared to an estimated median PFS of 4 months for patients receiving no treatment (placebo arm). The favorable results from the cabozantinib arm were robust based on various sensitivity analyses and consistent within relevant patient subgroups, including subgroups retrospectively identified as *RET* mutation positive, *RET* mutation negative, and *RET* mutation status unknown. In addition, there was a significantly higher overall response rate (27%) for cabozantinib-treated patients as compared to no responses in the placebo arm.

In a planned interim analysis, conducted after 44% of the total deaths for the final analysis of survival, and in an unplanned analysis conducted at FDA's request and submitted at the 120-day update, with 75% of the planned deaths for the final analysis, there was no evidence of significant improvement in overall survival for cabozantinib-treated patients. The estimated median survival times were 26 months for cabozantinib-treated patients and 20.3 months for placebo-treated patients.

The safety database of 289 patients included the results of the major efficacy trial and two additional, single-arm trials in patients with various cancers, treated with cabozantinib 140 mg daily. In the major efficacy trial, dose modifications occurred in the majority (86%) of patients; the most common adverse reactions resulting in dose modification were palmar-plantar erythrodysesthia syndrome, weight loss, decreased appetite, fatigue, diarrhea, stomatitis, asthenia and nausea.

There was no difference in overall survival between the two treatment arms, although four deaths in the cabozantinib arm were considered probably related to treatment (1 death due to fatal hemorrhage, 2 deaths in patients with esophageal fistula formation, and 1 death due to respiratory failure in a patient with hemorrhage and possible fistula). The most common serious adverse reactions of cabozantinib are gastrointestinal (GI) perforations, GI and non-GI fistulas, thrombotic events, hemorrhage, wound complications, hypertension, osteonecrosis, and reversible posterior leukoencephalopathy syndrome. The most common (≥ 30%) adverse reactions of cabozantinib are diarrhea, stomatitis, palmar-plantar erythrodysesthesia syndrome, weight loss, decreased appetite, nausea, fatigue, oral pain, dysgeusia, oral pain, depigmentation of hair, and hypertension.

The major issue considered during this review was the acceptability of the proposed dose in light of the adverse reaction profile and given the lack of a clear exposure-response relationship in exploratory analyses conducted by the Clinical Pharmacology reviewers. Based on this concern, a post-marketing trial will be required to explore the safety and activity of a lower dose of cabozantinib.

2. Background

Indicated population/available therapy

Medullary thyroid cancer arises from the parafollicular cells of the thyroid and is reported to account for 3-5% of estimated 56, 460 cases of cancers of the thyroid gland estimated to occur in 2012. [1,2] Approximately one-quarter of MTC are hereditary and mutations of the *RET* (REarranged during Transfection) gene occur in 95% of these hereditary MTC cases, while the proportion of sporadic MTC with RET mutations is reportedly lower (25%)[3]. Mutation of *RET* leads to constituitive activation of receptor tyrosine kinases, with downstream activation of pathways involved in cell proliferation. Cabozantinib is designed to target this pathway common to hereditary MTC and some cases of sporadic MTC,

Dr.Guisti notes in her review that doxorubicin is approved for the treatment of thyroid cancer, however the basis for this approval is not clear from current records and it is uncertain whether this approval applies to medullary thyroid cancer.

On April 6, 2011 Caprelsa (vendetanib), a small molecule inhibitor of the RET, the VEGFR2, and other kinases, was approved for "the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Use of vandetanib in patients with indolent, asymptomatic or slowly progressing disease should be carefully considered because of the treatment related risks of vandetanib."

[1] http://www.cancer.gov/cancertopics/pdq/treatment/thyroid/HealthProfessional/page7
[2] Pitt SC, Moley JF: Medullary, Anaplastic, and Metastatic Cancers of the Thyroid. Semin Oncol 37 (6): 567-579, 2010.
[3] Liu Z, Falola J, Zhu X, et al: Antiproliferative effects of Src inhibition on medullary thyroid cancer. J Clin Endocrinol Metab 89:3503-3509, 2004.

Vandetanib is a small molecule that inhibits multiple kinases including members of the epidermal growth factor receptor (EGFR) family, vascular endothelial cell growth factor (VEGF) receptors, rearranged during transfection (RET), protein tyrosine kinase 6 (BRK), TIE2, members of the EPH receptors kinase family, and members of the Src family of tyrosine kinases.

The approval was based on a single, double-blind, placebo-controlled, randomized (2:1) trial conducted in 331 patients with unresectable locally advanced or metastatic medullary thyroid cancer. The primary efficacy endpoint was progression-free survival, with supportive endpoints of overall survival and overall objective response rate. Tumor-based endpoints were determined by a centralized, independent blinded imaging review. At the time of investigator-determined disease progression, the treatment blind for the individual patient was broken and all patients were offered treatment with vandetanib. Following investigator-determined disease progression, 19% of the 231 patients initially randomized to vandetanib and 58% of the 100 patients initially randomized to placebo chose to take vandetanib.

The trial demonstrated a statistically significant improvement in progression-free survival [HR 0.35 (95% CI: 0.24, 0.53); p<0.0001], with a median PFS time of 16.4 months in the control arm and median not reached at the time of the final PFS analysis in the vandetinib arm, and a significantly higher overall response (44% vs. 1%) for patients randomized to vandetanib compared to those randomized to placebo. At the time of the PFS analysis, based on 100 PFS events, at which time the estimated median PFS time was 6.4 months in the placebo arm and estimated median PFS time in the vandetinib arm not reached, the survival data were not mature.

Vandetanib was approved under a Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use (ETASU) based on the risks of Torsades de pointes and sudden death due QT prolongation. In addition, Vandetanib labeling contains Warnings and Precautions describing the following additional clinically important adverse reactions: skin reactions and Stevens-Johnson Syndrome, interstitial lung disease, ischemic cerebrovascular events, hemorrhage, heart failure, diarrhea, hypothyroidism, hypertension, Reversible Posterior Leukoencephalopathy Syndrome, drug interactions, renal impairment, hepatic impairment, and Pregnancy Category D.

Regulatory History of the Cabozantinib Development Program

Clinical investigations for the medullary thyroid cancer development program were conducted primarily under IND (b) (4) (b) (4)

hile development program for medullary thyroid cancer (IND 113446) (b) (4)

July 13, 2005: (b) (4)

March 6, 2008: An EOP2 meeting for the medullary thyroid development program was held on March 6, 2008 Key agreements reached were:

- Progression-free survival may be an acceptable efficacy endpoint, depending on the magnitude of the treatment effect and risk:benefit ratio

- PFS should be evaluated both by investigators and by blinded central review; the primary analysis of PFS will be based on central review-determined PS events
- The trial was to detect a 50% improvement in PFS (HR 0.667) assuming median PFS times of 8 months in the placebo arm and 12 months in the treatment arm.
- FDA recommended against an interim analysis of PFS after 50% of the planned events due to concerns that the interim data may not produce an accurate and reliable estimate of the true treatment effects.
- The protocol will permit patients in the placebo arm to cross over to open-label therapy at the time of investigator-determined disease progression; given the unblinding at the time of disease progression, the analysis plan should detail how such patients will be handled in the analysis of PFS.
- The trial should be powered to detect an improvement in overall survival; FDA accepted Exelixis' proposal to conduct an interim analysis of survival at the time of the final PFS analysis. Exelixis will file an NDA based on the final PFS analysis and interim analysis of survival
- Claims derived from subject self-assessent and quality of life instruments need to be based on data collected with a validated instrument for this purpose.

The adequacy of the clinical pharmacology program for cabozantinib to support an NDA was discussed during EOP2 meetings (March 6, 2008 (b) (4) May 2009) and at the December 12, 2010 pre-NDA meeting.

June 6, 2008: SPA agreement letter issued for Protocol XL184-301, which provided the following answers to Exelixis' questions

- Sponsor's Question 1: Since the discussion with the Agency on 06 March 2008, Exelixis has re-evaluated the assumptions made for both treatment groups in XL184-301. The current study is designed to detect a larger increase in PFS (75% improvement, median 14 months for XL184 versus 8 months for placebo), and OS (50% improvement, median 33 months for XL184 versus 22 months for placebo), at the time of final analysis. To maximize the ability to evaluate the effect of XL184 on overall survival, subjects on the placebo arm will not be allowed to cross-over to receive XL184 upon disease progression. In addition, Exelixis does not plan on conducting an interim analysis on PFS…Exelixis believes that [data from Protocol XL184-001] support the proposed assumptions of a 75% and 50% improvement for PFS and OS, respectively, in the XL184 versus placebo groups. Does the Agency agree with the proposed assumptions for PFS and OS?

  FDA response: The available data appear to be too limited to allow for accurate estimates of PFS and OS improvements. We therefore neither agree nor disagree with your assumptions, but simply view them as a reflection of the amount of risk you are willing to accept. The magnitude of improvement in PFS and/or OS required for drug approval will be a review issue.

- Sponsor Question 2: Given the current assumptions for PFS and OS, and the concern for long-term repeated exposure to radiation, tumor assessments will be conducted every 12 weeks...Does the Agency agree with this proposal?

FDA response: Yes, this is acceptable.

- Question 3: Subjects with MTC who have either measurable or non-measurable disease will be eligible for Study XL184-301. The primary efficacy endpoint of progression-free survival will be based on modified RECIST criteria (provided as Appendix C in the protocol, as well as in the Independent Review Committee Charter), which defines how progression will be determined in subjects with MTC with measurable and non-measurable disease. Does the Agency agree with the proposal to include subjects with non-measurable disease?

  FDA Response: Because PFS is the primary endpoint, including patients with non-measurable disease is problematic. It adds to the heterogeneity of the patient population and it essentially creates two different sets of progression criteria on which the primary endpoint is based. We would therefore need assurance that the overall results are consistent between these two patient populations if general claims are to be made that apply to both populations...You may wish to minimize the number of patients enrolled with non-measurable disease for the reasons described above. Alternatively, if a substantial number of patients with non-measurable disease are allowed in the study, then the randomization should be stratified by patients' measurable disease status in order to prevent an imbalance between the treatment groups.

- Sponsor Question 5: As discussed with the Agency on 06 March 2008, Exelixis is planning to evaluate subject self-assessment parameters and disease-related symptom burden with XL184 treatment as compared with placebo, as per the MD Anderson Symptom Inventory (MDASI) Thyroid Module as an exploratory study objective. The MDASI Thyroid Module consists of 13 elements from the widely-used MDASI Core Module with 6 additional items developed specifically for the symptoms of patients with thyroid cancer. Supportive documentation for both the Core and Thyroid Modules is provided in this submission. Does the Agency agree that the MDASI Thyroid Module is an appropriate instrument to measure subject self-assessment parameters and disease-related symptom burden, (b) (4)

  FDA response: No. We do not agree. Insufficient information was submitted to support the validity of the MDASI thyroid module as a measure of disease-related symptom burden (b) (4)

December 12, 2010: A pre-NDA meeting was held for the medullary thyroid indication and the following key agreements were reached:

- Safety experience will be supported by the pharmacokinetic data and clinical study reports from Protocols XL184-001 and XL184-301, a QTc evaluation substudy conducted within Protocol XL184-301, a P-gp in vitro study report, population PK analysis based on data obtained in Protocols XL184-001, XL184-201, XL184-203, and XL184-301.
- FDA recommended that, in addition, a food effect study, organ impairment studies and drug-drug interaction studies should also be submitted in the NDA
- The proposed approach to data presentation in the ISE and ISS were acceptable to FDA

- FDA agreed that since the daily 100 mg (freebase) dose of XL184 administered in Protocol XL184-203 was lower than the daily 140 mg (freebase) dose (expressed as 175 *l*-malate salt weight) administered in the Protocol XL 184-301), but rather was equivalent to a daily dose of 125 mg (*l*-malate salt weight), expedited safety reports for patients treated under Protocol XL 184-203 were not required for submission in the NDA.

April 8, 2011: Fast-track designation was granted for "the investigation of XL184 for patients with unresectable, locally advanced, or metastatic medullary thyroid carcinoma (MTC)".

November 29, 2010: Orphan drug designation was granted for cabozantinib for the treatment of follicular, medullary and anaplastic thyroid carcinoma and metastatic or locally advanced papillary thyroid cancer.

March 4, 2011: A pre-NDA CMC meeting was held
- FDA accepted Exelixis' proposal to include Quality information in the NDA only for the two XL184 capsule strengths of (b) (4) which were administered in the Protocol XL 184-301; (b) (4)
- FDA agreed that the proposal to manufacture higher dose commercial capsules containing 80 mg (freebase weights) XL184 was reasonable, based on Exelisis justification that the difference between the clinical and planned commercial dosage strength (79 mg versus 80 mg) is small relative to the variance in mean exposures in subjects administered 175 mg (salt)/139 mg (freebase) and therefore not clinically relevant.
- The proposed starting materials appeared to be acceptable
- In response to the request for a biowaiver, FDA stated that as long as the to-be-marketed formulation is sufficiently similar to the clinical trial formulation(s), in terms of (b) (4) and proper controls are applied, a BE study would not be needed. Alternatively, the sponsor may choose to conduct a BE study.
- Regarding qualification of genotoxic impurities, Exelixis was advised to follow the appropriate ICH guidances and that impurities can be managed individually.
- The proposed specifications for drug substance and drug product and the stability testing data package appeared to be reasonable.
- (b) (4)

December 20, 2011: A second preNDA meeting was held at which the high-level summary results for safety and efficacy were available. Key agreements reached were:
- Agreement on the schedule for the rolling submission and contents of each submission
- Agreement on the content and format of the data to be included in the Quality, Clinical Pharmacology, Clinical, and Non-clinical sections
- Agreement on the contents of the 120-day safety update, to include an unplanned interim analysis of overall survival

The NDA was submitted as a rolling submission
- Non-clinical module submitted Dec. 21, 2011
- Quality module submitted March 9, 2012

- Last components of Quality module (stability data), last components of the Administrative module (proposed labeling), and Clinical data (efficacy, safety, pharmacokinetics) submitted May 25, 2012, and received May 29, 2012.

3. CMC

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. There were no microbiology deficiencies noted in the NDA submission. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months at ambient room temperature. All quality and compliance reviewers recommended approval and there are no outstanding CMC issues that preclude approval.

Cabozantinib, also referred to as XL184, is a synthetically-derived molecule; data provided in the application support that the manufacturing process is appropriately controlled and specifications for process intermediates and final product are adequately justified. The drug product, COMETRIQ, will be marketed in oral hard gelatin capsules containing 20 mg or 80 mg of cabozantininb freebase (roughly equivalent to 25 mg or 100 mg cabozantinib *l*-malate salt) in blister packs providing a 7-day supply of capsules providing a daily dose of 140 mg, 100mg, or 60 mg cabozantinib, or bottles containing 20-mg capsules.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

As noted in Dr. Brower's review, cabozantinib is a small molecule tyrosine kinase inhibitor (TKI) which inhibits multiple receptor- -based tyrosine kinases including RET, MET, VEGFR 2, VEGFR1, VEGFR3, FLT3, TIE2, Axl, TrkB and KIT at IC50 concentrations that are achievable in human subjects. The application also provided proof-of-concept data for RET inhibition in murine xenograft models, where cabozantininb administration was documented to inhibit RET phosphorylation in medullary thyroid cells in a dose-dependent manner.

The nonclinical development program was adequate to support the NDA, containing nonclinical studies assessing the pharmacology, safety pharmacology, chronic toxicology, and reproductive toxicology of cabozantinib. The pharmacology of cabozantinib itself was similar to that in humans, with the dog appearing to most closely approximate human pharmacokinetics, however the concentration of active metabolites of cabozantinib were substantially lower in animals than in humans requiring that a post-marketing study be required for to assess the potential genotoxicity, in an *in vitro* mutagenicity assay, of the M4 metabolite.

The most common toxicities of cabozantinib were predicted by chronic toxicology studies. Effects observed in dedicated studies in rats and dogs evaluating the effects of cabozantinib on fertility suggest that fertility may be impaired in cabozantinib-treated males and females. In safety pharmacology trials, cabozantinib did not inhibit hERG channel activity at relevant

concentrations and no effects on cardiovascular parameters were observed in dogs. In safety pharmacology studies conducted in rats, behavioral and physiological changes were not observed following single doses of up to 300 mg/kg cabozantinib and single doses of 900 mg/kg cabozantinib had no effects on respiratory parameters.

Cabozantinib was not mutagenic or clastogenic. Genotoxic impurities were considered adequately characterized, in light of the indicated patient population, in accordance with ICH S9. The four major metabolites of cabozantinib were not mutagenic but have not been assessed for induction of chromosomal aberrations. However, based on the potential for long-term survival in some patients with medullary MTC (median survival from diagnosis is X), the non-clinical review team has identified the requirement for 2-year carcinogenicity studies in rats and mice.

Embryofetal development studies were conducted in rats and rabbits. In both species, there was increased risk of post-implantation losses at cabozantinib exposures of < 1% (rats) and 9-11% (rabbits) of the human exposure at the recommended dose of 140 mg compared to controls. Additional findings includes cardiac anomalies, and dose-dependent increases in skeletal variations in rats and a dose-dependent decrease in fetal body weight, increases in the incidence of visceral variations and malformations including reduced spleen size and missing lung lobes in rabbits at exposures significantly lower than the human exposure at the recommended dose. Reproductive toxicity findings suggest that male and female fertility can be impaired by treatment with cabozantinib. Based on these findings, product labeling identifies this product as Pregnancy Category D. In addition, based on the potential for extended survival in some patients with medullary thyroid cancer, and the known pharmacologic effects of inhibition of MET and VEGF pathways which may result in altered bone development, a post-marketing requirement for a pre/post-natal developmental toxicity study has been identified.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

The pharmacokinetics of cabozantinib capsules and cabozantinib "powder in bottle" dosage forms were evaluated in healthy subjects and in patients with cancer. The application also contained the results of a population PK (PopPK) analysis of cabozantinib performed with data from 289 patients with solid tumors in clinical trials evaluating the regimen of 140 mg cabozantinib capsules. In the population PK analysis, the half-life of cabozantinib at steady state was approximately 55 hours, the oral volume of distribution is approximately 349 L, and clearance (CL/F) was estimated to be 4.4 L/hr. The median T_{max} was approximately 2-4 hours in cancer patients following a single oral dose. Mass balance studies in healthy subjects demonstrated that 54% of administered radioactivity was recovered in the feces and 27% was recovered in the urine. The dose proportionality of the cabozantinib capsules has not been evaluated, however dose-proportional AUC and Cmax were observed with the "powder in bottle" dosage form. Absolute oral bioavailability of cabozantinib capsule has not been determined. Significant increases in Cmax (41%) and AUC (57%) were observed when

cabozantinib was administered with a high-fat, high calorie meal in healthy subjects, thus product labeling states that cabozantinib should be taken without food/

The Clinical Pharmacology review team recommended that the dosing regimen in product labeling be based on pharmacokinetic modeling, with a proposed starting dose of 100 mg daily, to be increased to 140 mg or decreased to 60 mg based on observed toxicity. This recommendation was based on the observation that 86.4% of the patients in the major efficacy trial required dose modification (interruption, reduction, or termination), on exposure-response analyses suggesting that progression-free survival was similar across all quartiles for cabozantinib exposure, and a correlation observed between model-predicted steady state exposure ($AUC_{SS\ PRED}$) and time to first dose medication (shorter time with higher exposure). It is noted that there was no correlation between exposure and the incidence of the most common adverse reactions resulting in dose modification (palmar-plantar erythrodysesthesia or diarrhea). Dr. Jun concluded that "These E-R relationships for efficacy and safety suggest that a lower dose might be effective with improved tolerability; therefore, label should include a starting dose of 100 mg with a provision to increase the dose to 140 mg or decreased to 60 mg as tolerated."

Given the exploratory nature of the exposure-response analysis performed using the results for sparse PK sampling techniques in 200 patients per Table 5 of Dr. Jun's review, it is my opinion that the data are inadequate to support a recommended dose that has not been studied. As an alternative, the clinical and clinical pharmacology review teams have agreed that a trial to confirm that an alternative dosing regimen is safer and retains sufficient efficacy be required under the provisions of 505(o).

The results of the population PK analyses do not identify clinically relevant differences in exposures based on gender, age, or race (White versus non-White) and that the effect of mild and moderate renal impairment on clearance of cabozantinib is minimal. Since cabozantinib is cleared by the kidneys and metabolized, via CYP3A4, in the liver and formal studies of the pharmacokinetics of cabozantinib in patients with renal or hepatic organ impairment have not been conducted, the clinical pharmacology reviewer has stated that post-marketing trials to evaluate the pharmacokinetics of cabozantinib in patients with severe renal impairment and in patients with hepatic impairment are required. Pending the completion of the hepatic impairment trial, product labeling contains a Warning that cabozantinib is not indicated for the treatment of patients with hepatic impairment. In addition, product labeling contains recommendations to avoid use of strong CYP3A4 inducers or inhibitors in patients receiving cabozantinib, and proposes specific recommendations for dose modification based on the dedicated drug interactions studies of cabozantinib in patients taking strong CYP3A4 inducers or inducers. Dedicated studies have shown that cabozantinib exposure is increased by 38% when administered to subjects taking a strong CYP3A4 inhibitor and that cabozantinib exposure is decreased by 77% in subjects taking a strong CYP3A4 inducer.

Population PK studies were inconclusive regarding the effects of gastric pH modifying agents on cabozantinib pharmacokinetics. Since the solubility of cabozantinib is pH-dependent, the clinical pharmacology review team has stated that a post-marketing trial to conduct a dedicated

study assessing the effects on pH modifying agents on cabozantinib pharmacokinetics also be required.

The effects of cabozantinib on the QT interval were assessed in a dedicated substudy within the major efficacy trial. The IRQT consultant's assessment of this substudy was that no large increases in mean QT interval (>20 ms) were detected at steady state (pre-dose on Cycle 2, Day 1) compared to baseline values in the 166 cabozantinib-treated patients assessed on C2D1. The mean change was 11.3 ms (90% CI: 8.7, 13.95). There were no new changes in cardiac wave form morphology or new rhythms in patients with increased QT interval and no cabozantinib -treated patient had a QTcF >500 ms. These results have been described in the Clinical Pharmacology section of product labeling, however based on these data, no Warnings or Precautions are required.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

There were no issues raised during the review regarding the adequacy of the development program and efficacy data submitted to the NDA. Prior to submission of NDA 203756, the FDA met with Exelixis during an EOP2 meeting and preNDA meeting to discuss the scope and adequacy of the development program in medullary thyroid cancer. FDA agreed that arobust (statistically significant) treatment effect on progression-free survival of sufficient magnitude in a single trial (XL184-301), and characterization of the effects on overall survival, could be sufficient to support an NDA. The development program and outcomes are also similar to those that formed the basis of approval for another drug, vandetinib, in the treatment of medullary thyroid cancer. No concerns were identified with the data integrity for the efficacy results during this review, however as will be discussed in the next section, missing data and poorly written narratives of serious adverse events, made assessment of safety challenging. Finally, as discussed in sections 5 and 8 of this review, concerns were raised by both the clinical and clinical pharmacology reviewers regarding dose optimization in that the starting dose chosen for the Phase 3 trial was poorly tolerated, with 86% of patients requiring dose reduction in the treatment arm.

Trial Design

Efficacy in this NDA was obtained from a single international, randomized (2: 1), double-blind, placebo-controlled trial (Protocol XL184-301) conducted in patients with actively progressing, measurable or non-measurable metastatic medullary thyroid cancer (MTC). Enrollment of patients with non-measurable disease was capped at 31 patients (10% of the total planned enrollment). Key eligibility criteria were age 18 years or older, ECOG performance status 0-2, and documented progression of disease within the preceding 14 months prior to enrollment [the majority (89%) had actively progressing disease as determined by independent central review; per protocol amendment 2, the remainder were identified as

having actively progressing disease by the clinical investigator only]. There were no criteria regarding the number of prior lines of systemic treatment for MTC. Patients who received prior systemic anti-tumor therapy within 4 weeks of randomization, who had received radiation to ≥25% of bone marrow, with CNS metastases or spinal cord compression, with a history of clinically significant hematemesis, hemoptysis or other signs indicative of pulmonary hemorrhage, or with evidence of endobronchial lesions, were ineligible.

Patients were randomized (2:1) to receive 140 mg cabozantinib (equivalent to 175 mg *l* malate salt) or placebo as a single oral daily dose until disease progression or unacceptable toxicity after no more than two levels of dose reduction. Patients in the placebo arm were not crossed over to cabozantinib at the time of disease progression. Randomization was stratified by age (≤ 65 years vs > 65 years) and prior exposure to a tyrosine kinase inhibitor (prior treatment vs no prior exposure).

Tumor assessments were to be performed approximately every 12 weeks until disease progression, as determined by the investigator per mRECIST; all patients were followed post-progression for survival.

The primary objective of XL184-301 was to assess progression-free survival (PFS) as determined by an independent central review committee (IRC), masked to treatment assignment.

Key secondary objectives were:
- overall survival (OS);
- objective response rate (ORR) and duration of response;
- safety and tolerability of cabozantinib, including effects on QTc;
- pharmacokinetics of cabozantinib.

Exploratory endpoints that were also evaluated included:
- change in serum levels of calcitonin and of carcinoembryonic antigen (CEA) from baseline to end-of -treatment;
- retrospective testing and assessment of the treatment effects on PFS in subgroups defined by RET mutation status;
- patient self-assessment using the MD Anderson Symptom Inventory (MDASI) Thyroid Module (THY).

The sample size for the efficacy trial was based on the following assumptions: 138 PFS events were required to have 90% power to detect a hazard ratio (HR) of 0.571 using the log-rank test, as a 2-sided significance level of 5%, provided that the median PFS times were 8 months for the placebo arm and 14 months in the cabozantinib arm. The sample size assumptions for the overall survival analysis, a key secondary endpoint for which FDA requested that the trial be designed to assess, were that 217 deaths were required to have 80% power to detect a HR of 0.667 using a log-rank test at a 2-sided overall significance level of 4%, provided that the median survival times were 22 months in the placebo arm and 33 months in the cabozantinib arm. A single interim analysis of survival was to be performed at the time of the final analysis of PFS, when an estimated 67 deaths were expected; the overall alpha level for the analysis of

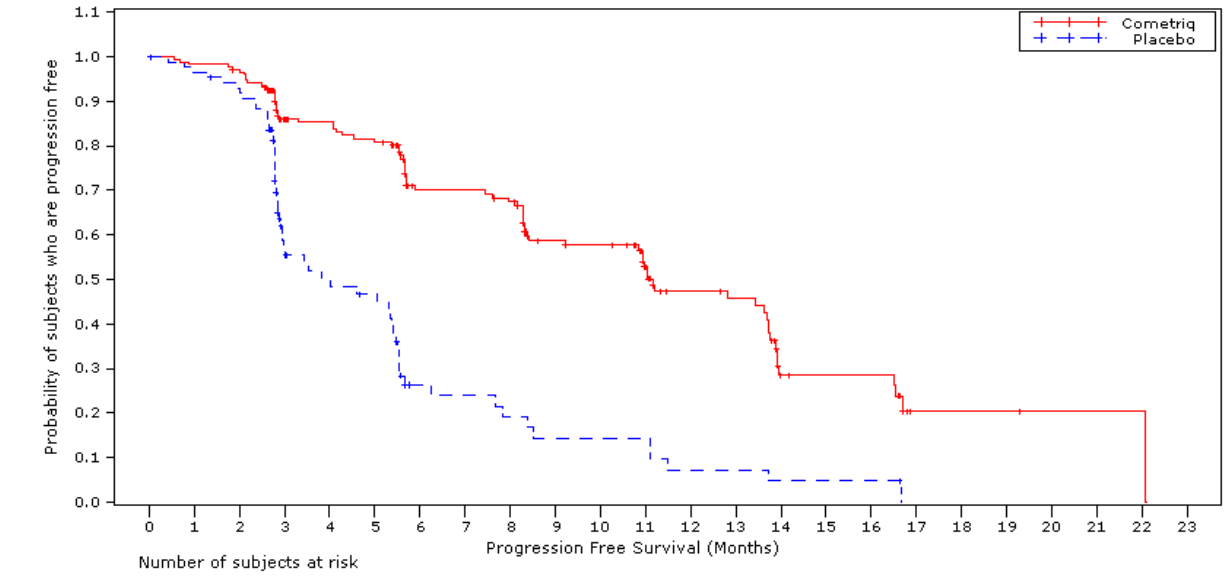
survival was maintained using the Lan-DeMets O'Brien-Fleming alpha spending function, with a significance level of 0.00006 for interim analysis of survival. Overall response rates were to be compared between the treatment arms, with an overall significant level of 0.01, two-sided. The primary analysis of ORR based on the IRC determined response status was to be performed at the time of the primary analysis of PFS.

Results

A total of 330 patients (219 in Cabozantinib and 111 in placebo arm) were registered and randomized; these patients were enrolled at 90 clinical sites in 23 countries in Europe, North America, Middle East, South America and Asia. The data cut-off date for efficacy analyses was June 15, 2011; at this time, nearly half the patients (45%) on the cabozantinib arm were continuing to receive investigational study drug, while 14% of placebo-treated patients were receiving investigational study drug.

The median age of the study population was 55 years, with 72 patients (22%) age 65 years or older, 67% were male, 89% were White, 56% were enrolled from European sites and 31% from sites in North America, 6% had an ECOG PS of 2, 40% ECOG PS 1, and 54% an ECOG PS of 0. With regard to disease status, 94.5% had measureable disease at entry and all but one patient had metastatic disease at entry; 95% had AJCC stage IVc disease. The most common sites (≥ 50%) of metastatic disease, in descending order were lymph nodes, liver, lung, and bone, 58% had no prior systemic treatment for MTC while 26% had received 2 or more prior lines of therapy. Sixty-eight (21%) patients had received a prior tyrosine kinase inhibitor. Twenty (6%) patients had hereditary MTC, 86% had sporadic MTC, and for 8% the information was not provided. Evaluation for RET mutation status was conducted retrospectively using a non-validated assay, with results provided for 69% of the study population. Among these 289 patients, 55% were reported to have RET mutations.

The efficacy results, as presented in the statistical review, are abstracted and presented below



Primary and Secondary Efficacy Endpoints In Protocol XL184-301		
	Cabozantinib (n=219)	Placebo (n=111)
Final analysis - progression-free survival		
Number of PFS events	79	60
Median	11.2 mos	4.0 mos
Hazard Ratio	0.28	
95% CI[1]	(0.19, 0.40)	
p-value[2]	<0.0001	
Interim analysis - overall survival		
Number of OS events	66	30
Median	21.1 mos	NR[3]
Hazard Ratio	0.98	
95% CI	(0.64, 1.54)	
p-value[2]	0.99	
FDA-requested update - overall survival		
Number of OS events	103	59
Median	26.0	20.3
Hazard Ratio	0.825	
95% CI	(0.60, 1.14)	
p-value[2]	0.24	
Final analysis – overall response rate		
Number of Partial Responses[4]	58	0
Overall Response Rate	27%	0
95% CI	(20.8, 32.9)	NA[5]
p-value[6]	<0.0001	
Median duration of response	14.7 mos	NA

[1] confidence intervals
[2] stratified log-rank test
[3] not reached
[4] All responses were partial responses
[5] not applicable
[6] stratified Cochran-Mantel-Haenszel test

The treatment effect on PFS was consistent across both demographic subgroups (age, gender) and prognostic subgroups (ECOG PS 0 vs. 1 vs. 2), prior lines of therapy (0 vs. 1 vs. ≥2), prior treatment with TKI (yes vs. no) and by RET mutation status. In patients retrospectively identified to have a RET mutation, the hazard ratio was 0.23 (95% CI 0.14, 0.38), while in those identified as RET mutation negative, the hazard ratio was 0.44 (95% CI 0.15, 1.30) and in those without assessment of RET mutation status, the hazard ratio was 0.30 (95% CI 0.16, 0.56). Due to the retrospective nature of the RET mutation testing, convenience sample (31% missing data), and lack of validation of the assay, these results should be viewed cautiously but

do suggest that the presence of RET mutation may not be required to achieve a treatment effect. Treatment effects were observed both in patients with hereditary MTC [HR 0.09 (95% CI 0.01, 0.82)] and in those with sporadic MTC [HR 0.32 (95% CI 0.22, 0.46)].

8. Safety

The size of the safety database, which was primarily limited to the major efficacy trial and two additional trials that evaluated the safety of cabozantinib monotherapy in 295 cabozantinib-treated patients, is small but adequate to identify serious adverse reactions. Comparative safety data are available only from the major efficacy trial, with comparison of adverse events in 214 cabozantinib-treated patients with those observed in 109 placebo-treated patients. As noted in Dr. Guisti's review, "Because of the small numbers of patients enrolled in XL184-001 and XL184-201 and the lack of a comparator arm in these trials, data from these trials were not pooled with data from XL184-301. No new or unexpected safety events were identified from these trials."

The quality of the safety database for the major efficacy trial was adequate to assess for severe (Grades 3-4) and serious adverse reactions; however, missing data (e.g., blood pressure measurements) for expected adverse reactions (e.g., incomplete collection of serial blood pressure data in a drug expected to result in hypertension based on known mechanism of action) may have led to underestimation of the incidence of less severe (Grades 1-2) adverse reactions. On review of case narratives, the quality of some of the narratives were poor, with failure to include sufficient documentation to confirm the diagnosis of or characterize the outcomes for certain reported serious adverse reactions (e.g., reported case of hemolytic uremic syndrome lacked documentation for this diagnosis; reported case of pancytopenia failed to characterize duration, bone marrow assessment).

The data from the major efficacy trial reflect exposure to cabozantinib for a median of 188 days and median relative dose intensity of 65% (to the intended dose of 140 mg daily). It is notable that the median relative dose intensity was 87% for patients in the placebo-arm, suggesting that dose reductions treatment-emergent adverse reactions in both treatment arms may have occurred for reasons other than treatment-induced toxicity. In the cabozantinib arm, the most common adverse events leading to dose reduction were palmar-plantar erythrodysesthia syndrome, weight loss, decreased appetite, fatigue, diarrhea, stomatitis, asthenia and nausea.

There was no difference in overall survival between the two treatment arms; the number of adverse reactions resulting in death during treatment or within 30 days of the last dose of study drug was comparable. Four deaths in the cabozantinib arm were considered probably related to treatment (1 death due to fatal hemorrhage, 2 deaths in patients with esophageal fistula formation, and 1 death due to respiratory failure in a patient with hemorrhage and possible fistula), while the rate of deaths due to sepsis or aspiration pneumonia were similar between the treatment arms.

The following table provides a listing of selected adverse reactions, occurring more frequently in cabozantinib-treated patients and with an overall per-patient incidence of ≥5% in cabozantinib-treated patients.

Per-Patient Incidence of Selected Adverse Reactions in Protocol XL184-301 Occurring at a Higher Incidence [Between Arm Difference of ≥ 5% (All Grades) or ≥ 2% (Grades 3-4)] in Cabozantinib-Treated Patients				
MedDRA System Organ Class and Preferred Terms	Cabozantinib (n=214)		Placebo (n=109)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
GASTROINTESTINAL DISORDERS				
Diarrhea	63	16	33	2
Stomatitis[1]	51	5	6	0
Nausea	43	1	21	0
Oral pain[2]	36	2	6	0
Constipation	27	0	6	0
Abdominal pain[3]	27	3	13	1
Vomiting	24	2	2	1
Dysphagia	13	4	6	1
Dyspepsia	11	0	0	0
Hemorrhoids	9	0	3	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Fatigue	41	9	28	3
Asthenia	22	6	15	1
INVESTIGATIONS				
Decreased weight	48	5	10	0
METABOLISM AND NUTRITION DISORDERS				
Decreased appetite	46	5	18	2
Dehydration	7	2	2	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Arthralgia	14	1	7	0
Muscle spasms	12	0	5	0
Musculoskeletal chest painN	9	1	4	0
NERVOUS SYSTEM DISORDERS				
Dysgeusia	34	0	6	0
Headache	18	0	8	0
Dizziness	14	0	7	0
Parathesia	7	0	2	0
Peripheral sensory neuropathy	7	0	0	0
Peripheral neuropathy	5	0	0	0

Per-Patient Incidence of Selected Adverse Reactions in Protocol XL184-301 Occurring at a Higher Incidence [Between Arm Difference of ≥ 5% (All Grades) or ≥ 2% (Grades 3-4)] in Cabozantinib-Treated Patients				
MedDRA System Organ Class and Preferred Terms	Cabozantinib (n=214)		Placebo (n=109)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
PSYCHIATRIC DISORDERS				
Anxiety	9	0	2	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Dysphonia	20	0	9	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
PPES[4]	50	13	2	0
Hair color changes/ depigmentation	34	0	1	0
Rash	19	1	10	0
Dry skin	19	0	3	0
Alopecia	16	0	2	0
Erythema	11	1	2	0
Hyperkeratosis	7	0	0	0
VASCULAR DISORDERS				
Hypertension	33	8	4	0
Hypotension	7	1	0	0

[1] Includes the following terms: stomatitis, apthous stomatitis, mouth ulceration, mucosal inflammation
[2] Includes the following terms: oral pain, oropharyngeal pain, glossitis, burning mouth syndrome, glossodynia
[3] Includes the following terms: abdominal pain, abdominal pain lower, abdominal pain upper, abdominal rigidity, abdominal tenderness, esophageal pain
[4] Palmer-plantar erythrodythesia syndrome

Reporting of hypertension as an adverse reaction appears to underestimate the true incidence. An assessment of hypertension was conducted using the recorded vital signs during study visits, applying the criteria for treatment of hypertension as published by the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JAMA 2003: 289:2560). An analysis of hypertension based on the highest recorded blood pressure measurements at two visit, graded by the JNC classification system reveals a higher incidence of hypertension (stages 1 and 2) requiring medical intervention for cabozantinib-treated patients (61% vs. 30%).

Per-Patient Incidence of Hypertension by Treatment Group Based on the Joint National Committee Classification System		
Hypertension, JNCC[1] Stage	**Cabozantinib N = 211[3]**	**Placebo N = 107[3]**
Normal: Grade 0: Systolic < 120 mmHg and Diastolic < 80 mmHg	4	15
Prehypertension: Systolic ≥ 120 mmHg or Diastolic ≥ 80 mmHg	34	54
Stage 1: Systolic ≥ 140 mmHg or Diastolic ≥ 90 mmHg	46	25
Stage 2: Systolic ≥ 160 mmHg or Diastolic ≥ 100 mmHg	15	5
Malignant: Diastolic ≥ 120 mmHg	0	0

[1]Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, JAMA 2003: 289:2560
[2]Subjects classified by highest category based on all recorded blood pressure readings beginning after the first dose through 30 days after last dose.
[3]Patients with at least two blood pressure measurements after the first dose

Abnormal laboratory findings attributable to cabozantinib are displayed in the following table. With the exception of hypocalcemia, the differences in severe or life-threatening (Grade 3-4) laboratory abnormalities were trivial and unlikely to be clinically relevant.

Per-Patient Incidence of Abnormal Laboratory Findings Occurring at a Higher Incidence [Between Arm Difference of ≥ 5% (All Grades) or ≥ 2% (Grades 3-4)] in Cabozantinib-Treated Patients				
	Cabozantinib (n=214)		Placebo (n=109)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Chemistries				
Increased AST[1]	86	3	35	2
Increased ALT[2]	86	6	41	2
Hyperbilirubinemia	25	2	14	5
Increased ALP[3]	52	3	35	3
Hypophophatemia	28	3	10	1
Hypocalcemia	52	12	27	3
Hypomagnesemia	19	1	4	0
Hypokalemia	18	4	9	3
Hyponatremia	10	2	5	0
Hematologic				
Lymphopenia	53	16	51	11
Neutropenia	35	3	15	3
Thrombocytopenia	35	0	4	3

[1] aspartate aminotransferase
[2] alanine aminotransferase
[3] alkaline phosphatase

REMS

Exilixis did not propose a REMS or Risk Management Plan, however they did submit a Medication Guide as patient labeling and proposed that Dear Healthcare Professionals/Dear Professional Society letters titled "Important Safety Information" containing the proposed indications and listing serious risks (as bulleted below) be issued following approval.

- Gastrointestinal (GI) perforations, GI and non-GI fistulas, and abscesses have been observed. Patients should be evaluated for potential predisposing risks for these events.
- Thrombotic events and hemorrhage have been observed. COMETRIQ should be used with caution in patients at risk for these events.
- Wound complications, hypertension, osteonecrosis, and reversible posterior leukoencephalopathy syndrome have been observed.
- An increase from baseline in QTcF of 10 - 15 ms was observed in a controlled clinical study with cancer patients.
- Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant while receiving treatment with COMETRIQ and for 4 months after discontinuation of COMETRIQ treatment.

The clinical review team recommended that the Medication Guide be retitled as a Patient Package Insert, but otherwise agreed with the contents of the proposed Dear Healthcare Provider and Professional letters, as part of the launch information to alert prescribers and healthcare practitioners to these serious risks. The clinical review team and the DRISK consultant agreed that a REMS with Elements to Assure Safe Use was not required to ensure safe use of cabozantinib. While the adverse reaction profile is serious, it is similar to that observed with other products affecting the VEGF pathway that have been approved without a REMS.

PMRs and PMCs

The clinical review team has proposed a post-marketing requirement to conduct a trial to determine whether a lower dose would have similar efficacy and lesser toxicity than the dose administered in Protocol XL184-301. I concur that this PMR should be required, given the need for dose modifications in the majority of patients and the exploratory exposure-response analyses conducted by the Clinical Pharmacology review staff, which could not identify a clear exposure-response relationship over the range of exposures in this major efficacy trial.

9. Advisory Committee Meeting

The NDA for this new molecular entity was not presented to the Oncologic Drugs Advisory Committee for all of the following reasons: 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.

10. Pediatrics

This application is not subject to the requirements of the Pediatric Research Equity Act (PREA), since cabozantinib was granted orphan drug designation status on November 29, 2010 for the treatment of follicular, medullary, and anaplastic carcinoma and metastatic or locally advanced papillary thyroid cancer.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: Cometriq (cabozantinib) capsules
  The proposed proprietary name conditionally accepted at stated in the December 6, 2011 letter issued under IND (b) (4) and confirmed within 90 days prior to the action date to be acceptable by the DMEPA consultant. No other review team members raised objections to this proprietary name and the OPDP consultant also deemed this name acceptable.

- Physician labeling (major issues that were discussed, resolved, or not resolved)
  - Boxed Warning: At FDA's request, a Boxed Warning was added to the label for the treatment-related adverse reactions of Hemorrhage and Perforation/Fistula Formation, which resulted in significant morbidity and treatment-related mortality.
  - Indications and Usage: Indication statement revised to reflect population studied, which included only patients with metastatic disease with evidence of disease progression over the preceding 14 months prior to entry.
  - Dosage and Administration section: edited for command language; Dose modification subsection expanded to identify when treatment should be permanently discontinued (as stated in proposed Warnings/Precautions) and to provide information on dose modifications in patients who require concomitant treatment with either strong CYP3A4 inhibitors or strong CYP3A4 inducers. These recommendations are based on dedicated drug interaction studies which demonstrate clinically important effects on cabozantinib exposure. In addition, statement added that COMETRIQ use is not recommended in patients with hepatic impairment based on lack of necessary safety information to determine a safe and effective dose. .
  - Dosage Forms and Strength: Editorial changes for clarity

- Contraindications: Modified to state "none" as there are no clear cases of significant hypersensitivity to cabozantinib.
- Warnings and Precautions
  - Edited to include information on the incidence of the risk, where known, as per FDA Guidance to Industry on Product Labeling for this section and edited for "command language"
  - Added new subsections for palmar-plantar Erythrodysesthesia and proteinuria as clinical studies demonstrated a signficant risk (>1%) of serious adverse reactions for which monitoring and appropriate dose modification are needed to mitigate serious risks.
  - Moved information on "Drug Interactions' to the Clinical Pharmacology and Dosage and Administration sections, where specific directions for use or avoidance will mitigate risks; inclusion of such information in the Dosage and Administration section is also consistent with the current policies in the Office of Clinical Pharmacology.
  - Retitled "Pregnancy" subsection to "Embryofetal Toxicity" which more clearly identifies the risks; modified to include specific information on potential risks.
- Adverse Reactions
  - Added references to serious adverse reactions further described in the Warnings and Precautions section of the labeling, in accordance with FDA Guidance for Industry on Product Labeling for this section.
  - Simplified tables (to provide incidence but not specific patient numbers), reorganized by System Organ Class, and removed adverse reactions that do not occur more frequently in cabozantinib-treated patients (≤5% higher incidence for cabozantinib group for Grade 1-4 or ≤ 2% for Grade 3-4 toxicity) in accordance with FDA Guidance for Industry on Product Labeling.
  - Moved up text regarding adverse reactions resulting in death, treatment discontinuation or dose modification to introductory paragraphs for section 6.1; provided comparative data from placebo-treated group, where missing from proposed PI.
- Drug Interactions: Edited for brevity, essential information, and consistency with Office of Clinical Pharmacology policies for data to be included in this section. Removed information on P-gp substrates as the effects of cabozantinib on P-gp substrates is not predicted to be clinically important.
- Use in Specific Populations
  - The pregnancy category ((b) (4) proposed by Exelixis) was revised to Category D based on the animal studies and OHOP/DHOT's standard practice for drugs used to treat cancer.
  - Subsections on Risk Summary and Animal Data, with an expanded description on the non-clinical findings were added to section 8.1, based on the Pediatric and Maternal Health Staff consultant review and current PMHS policy on data presentation in this section of product labeling.
  - Geriatric Use subsection revised for consistency with current FDA Guidance to Industry on Product Labeling, which describes experience in less than 100 patients age 65 years and older as inadequate to characterize treatment effects in this subpopulation.

    - Addition of new subsection, titled Females and Males of Reproductive Potential, providing contraceptive advice and describing potential risks of infertility, based on the Pediatric and Maternal Health Staff consultant review and current PMHS policy on data presentation in this section of product labeling.
    - Subsection on Hepatic Impairment revised to include laboratory parameters defining hepatic impairment and statement that COMETRIQ is not recommended for use in patients with hepatic impairment. This statement is based on the known hepatic metabolism of cabozantinib and lack of data in patients with hepatic impairment, thus a potentially safe and effective dose cannot be identified,
    - Subsection on Renal Impairment revised to provide guidance on dosing in patients with mild-to-moderate renal impairment based on the results of the population PK analysis.
- Overdosage
    - This section will be revised to describe the findings in a patient with unintentional overdose (as described in SAE narrative report) and to remove recommendations for patient management that are theoretical (i.e., not supported by clinical experience).
- Description
    - Removed references to mechanism of action as this is described in section 12 of the label
- Clinical Pharmacology
    - Section 12.1 edited for brevity and to remove references to (b) (4)
    - Section 12.2 edited for brevity; subsections on absorption and distribution, on metabolism and elimination, and on effects of gender, age, and race were combined; added subsections on available pharmacokinetic data in subjects with renal impairment, hepatic impairment, pediatric patients, and subsections describing predicted drug interactions based on CYP enzyme induction or inhibition and P-gp inhibition.
    - Added new section, 12.6, on effects on cardiac electrophysiology describing effects of cabozantinib on the QT interval and cardiac conduction.
- Non-Clinical Toxicology
    - Section 13.1 expanded to include information on exposure, as a fraction of the human exposure at the recommended dose, for non-clinical studies assessing cabozantinib effects on fertility. Moved recommendations regarding contraceptive use from section 13.1 to section 8.6.
- Clinical Studies
    - Provided greater detail on key eligibility criteria, randomization plan, treatment plan.
    - Added information characterizing study population (baseline demographic and tumor characteristics
    - Efficacy data described in text rather than in tabular format
    - (b) (4)
- References: Deleted; (b) (4) .

- Storage and Handling
  - Edited for brevity and essential information
- Patient Counseling
  - Modified for essential information and removal statements that are not supported by data (b) (4)

- Carton and immediate container labels: All proposed revisions by ONDQA and DMEPA have been incorporated into carton & container labeling.

- Patient labeling/Medication guide: Exelixis proposed a Medication Guide; at FDA's suggestion, the Medication Guide was changed to Patient Package Insert, which was modified to provide information at 6th grade reading level, using FDA standard format (Question/Answer) for patient labeling.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I recommend approval

- Risk Benefit Assessment
  Medullary thyroid cancer (MTC) is an indolent cancer, with approximately 3000 new cases expected in 2012. New cases are frequently identified due to tumor secretion of calcitonin rather than local symptoms; however, for patients who cannot be cured with surgical resection of the thyroid, symptoms due to local and distant metastatic disease become equally important as endocrinologic symptoms and result in significant morbidity. Prior to the approval of vandetinib in 2011, there were no FDA-approved agents for metastatic MTC and off-label use of antineoplastic agents yielded limited activity, thus there was a clear unmet need for new treatments.

  In a well-conducted and well-controlled trial, cabozantinib was shown to significantly prolong the time to disease progression or death, with an improvement in median PFS time of 7 months, and treatment results in durable tumor responses (27% ORR with median duration of response of 14.7 months). The magnitude of these effects is clinically important and statistically robust. The risks of cabozantinib therapy are also clinically important, but are well-understood risks common to many antineoplastic agents and considered generally acceptable to patients and healthcare providers. The most common serious adverse reactions of cabozantinib are gastrointestinal (GI) perforations, GI and non-GI fistulas, thrombotic events, hemorrhage, wound complications, hypertension, osteonecrosis, and reversible posterior leukoencephalopathy syndrome. The most common (≥ 30%) adverse reactions of cabozantinib are diarrhea, stomatitis, palmar-plantar erythrodysesthesia syndrome, weight loss, decreased appetite, nausea, fatigue, oral pain, dysguesia, oral pain, depigmentation of hair, and hypertension.

All review team members recommended approval. Based on the information discussed above, I find that the application provides substantial evidence of effectiveness and that the risks:benefit analysis is favorable.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  The applicant did not propose a REMS and the review team did not identify the need for a REMS to ensure safe use of cabozantinib. I concur with the review team's recommendation that a REMS is not required to ensure safe use, as drugs with similar adverse reactions profiles are being administered in clinical practice without a REMS.

- Recommendation for other Postmarketing Requirements and Commitments
  The review team has identified the need for the following post-marketing requirements to further assess the safety of cabozantinib. The rationale for these PMRs are discussed in Sections 4, 5, and 9 of this summary review.

  - An *in vitro* mutagenicity study to assess the genotoxic effects of the M4 metabolite
  - A 2-year carcinogenicity study in rats
  - A 2-year carcinogenicity study in mice
  - A reproductive toxicology study to assess pre-and post-natal effects on bone and tooth growth and development.
  - A pharmacokinetic study in patients with severe renal impairment
  - A pharmacokinetic study in patients with hepatic impairment
  - A trial to determine if a lower dose of cabozantinib results in a better toxicity profile and tolerability with non-inferior efficacy to the dose of 140 mg daily. The primary objectives would be to show less toxicity, based on comparison of the overall incidence of common adverse reactions and of serious/severe adverse reactions, with the lower dose to the 140 mg dose with demonstration of non-inferior activity (progression-free survival and overall response rate).

  One potential post-marketing commitment was identified, which had been previously conveyed to Exelixis in FDA's December 6, 2011 letter issued under IND (b) (4)

  > "We note that the proposed capsule strengths (20 mg and 80 mg) are inconsistent with the proposed dosing regimen of 140 mg daily. It is not possible to achieve the proposed daily dose when using the 80 mg capsules without the concomitant use of 20 mg capsules, or without taking seven of the 20 mg capsules. The use of two strengths will be prone to medication error since one cannot achieve a daily dose using only the 80 mg capsules, and seven capsules per day places a large pill burden on patients and may lead to non-compliance. Please consider revising your capsule strengths to better reflect your proposed daily dose."

  In light of the PMR for evaluation of a lower, potentially safer, dose, this request for alternative packaging will not be conveyed, but may be re-considered following completion of the PMR, since the recommended dose may change based on the results of the PMR trial.

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/s/

PATRICIA KEEGAN

11/28/2012

Originally uploaded November 20, 2012; replaced to address missing word in original version that providing conflicting information regarding conclusions