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*APPLICATION NUMBER:*

**203756Orig1s000**

**OFFICE DIRECTOR MEMO**

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
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:	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Division Director	Patricia Keegan
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

## 1. Introduction

Cabozantinib is an inhibitor of multiple tyrosine kinases, including RET, MET, and VEGFR2. Cabozantinib in medullary thyroid cancer (MTC) is 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 vandetanib, which was approved for the treatment of metastatic MTC in 2011, based on a similarly designed trial and endpoints (progression-free survival and durable objective response rate) as cabozantinib.

This 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 MTC. 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 compared to 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 with 75% of the planned deaths for the final analysis), there was no evidence of significant improvement in overall survival (OS) 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 erythrodysesthesia syndrome, weight loss, decreased appetite, fatigue, diarrhea, stomatitis, asthenia and nausea.

There was no difference in OS 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 ( $\geq 30\%$ ) 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.<sup>1,2</sup> 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%)<sup>3</sup>. Mutation of *RET* leads to 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.

On April 6, 2011 Caprelsa (vandetanib), an inhibitor of the RET, 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.” 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.

## 3. CMC

There are no outstanding CMC issues that preclude approval. Chemistry reviewers have provided an overall 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.

## 4. Nonclinical Pharmacology/Toxicology

There are no outstanding pharmacology/toxicology issues that preclude approval.

This NDA contained 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; 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 of the M4 metabolite.

Studies in rats and dogs 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.

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<sup>1</sup> <http://www.cancer.gov/cancertopics/pdq/treatment/thyroid/HealthProfessional/page7>

<sup>2</sup> Pitt SC, Moley JF: Medullary, Anaplastic, and Metastatic Cancers of the Thyroid. *Semin Oncol* 37 (6): 567-579, 2010.

<sup>3</sup> 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.

Cabozantinib was not mutagenic or clastogenic. Genotoxic impurities were considered adequately characterized. 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 nonclinical 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

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. Results from a population PK analysis demonstrate that 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<sub>max</sub> 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 C<sub>max</sub> were observed with the "powder in bottle" dosage form. Absolute oral bioavailability of cabozantinib capsule has not been determined. Significant increases in C<sub>max</sub> (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 PK 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<sub>SS PRED</sub>) 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 Dr. Keegan's 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 postmarketing trial is required to confirm that an alternative dosing regimen is safer and retains sufficient efficacy.

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