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.

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