CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208692Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	4/25/2016
From	Geoffrey Kim
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	208692 N/A
Applicant	Exelixis, Inc.
Date of Submission	December 22nd, 2015
PDUFA Goal Date	June 22nd, 2016
Proprietary Name / **Non-Proprietary Name**	CABOMETYX™ (cabozantinib)
Dosage Form(s) / Strength(s)	60mg, 40mg, 20mg tablets
Applicant Proposed Indication(s)/Population(s)	CABOMETYX is indicated for the treatment of advanced renal cell carcinoma (RCC) in patients who have received (b) (4) prior therapy.
Action/Recommended Action for NME:	Approval
Approved/Recommended Indication/Population(s) (if applicable)	CABOMETYX is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy

Material Reviewed/Consulted	Names of discipline reviewers/Team Leaders
Regulatory Project Manager	Rajesh Venugopal/Christy Cottrell
Medical Officer Reviewer	Harpreet Singh and Michael Brave/ Julia Beaver
Statistical Review	Joyce Chen/ Shenghui Tang
Pharmacology Toxicology Review	Elias Zahalka/ Todd Palmby
CMC Review	Xing Wang – Drug Product and Substance Xiao Chen/ Anamitro Banerjee(Acting Branch Chief) – Drug Product
Micro process Reviewer	Ying Zhang/Jennifer Maguire
Facilities	Laura Fontan/Zhihao Peter Qiu
Biopharmaceutics	Fang Wu/Kimberly Raines
Clinical Pharmacology Review	Pengfei Song/ Qi Liu
Pharmacometrics Review	Chao Liu/ Yaning Wang
DMPP/OPDP	Nazia Fatima/Jessica Cleck Derenick
OSI	Lauren Iacono-Connors/ Susan Thompson
OSE/DMEPA	Tingting Gao/Alice (Chi-Ming) Tu
OSE/DRM	Carolyn Yancey/ Naomi Redd
OSE RPM	Frances Fahnbulleh
DEPI	Steven Bird
Patient Labeling	Rowe Medina/Barbra Fuller
Safety	Susan Jenny/ Katherine Fedenko

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

I concur with the Benefit-Risk Assessment that was made by the clinical and statistical teams. Based on the results of Study XL184-308, a favorable benefit-risk profile has been demonstrated for patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy. The regulatory action for this supplement is approval. As summarized by the clinical team:

"The recommendation for approval of cabozantinib is based on the results of Trial XL-184308, a multicenter, open-label, international, randomized (1:1) trial of cabozantinib versus everolimus in adult patients with advanced renal cell carcinoma who have had one prior VEGF therapy. Patients were stratified by the number of prior of VEGFR targeting therapies and number of risk factors per Memorial Sloan-Kettering Cancer Center prognostic criteria for previously treated patients with RCC.

Patients (n=658) were randomized and treated with either cabozantinib 60 mg orally daily (n=330) or everolimus 10 mg orally daily (n=328) until disease progression or unacceptable toxicity. Patients on both arms who had disease progression could continue treatment at the discretion of the investigator. The primary endpoint was PFS among the first 375 randomized patients (PITT population), by IRC-determined RECIST criteria. There was a statistically significant improvement in PFS for patients in the cabozantinib arm compared with the everolimus arm, with a 3.6 month difference in median PFS (7.4 vs. 3.8 months). The hazard ratio adjusted for stratification factors was 0.59 (95% CI: 0.46, 0.76; stratified log-rank p-value < 0.0001) per eCRF and 0.58 (95% CI: 0.45, 0.74; stratified log-rank p-value < 0.0001) per IVRS. Key secondary endpoints were OS and objective response rate (ORR) in the Intent-to-Treat population (ITT). Median OS in the ITT population was 21.4 and 16.5 months in the cabozantinib and Median OS in the ITT population was 21.4 and 16.5 months in the cabozantinib and everolimus arms, respectively [HR 0.66 (95% CI: 0.53, 0.83); p=0.0003]. Confirmed ORR was 17% (95% CI: 13, 22) in the cabozantinib arm and 3% (95% CI: 2, 6) in the everolimus arm.

Safety was evaluated in 331 patients treated with cabozantinib. The most common (greater than or equal to 20%) adverse reactions included diarrhea, fatigue, nausea, vomiting, constipation, abdominal pain, decreased appetite, hypertension, rash, palmarplantar erythrodysesthesia, weight decreased, and dygeusia. Serious adverse events were reported in 40% of patients. The most common serious adverse events (greater than or equal to 2%) were abdominal pain, pleural effusion, diarrhea, nausea, and anemia. Fifteen deaths were reported within 30 days of the last cabozantinib dose. Eight of the deaths were attributed to progressive disease, five deaths were due to cognitive deterioration, pneumonia, hemorrhage, cardiac failure, and urosepsis respectively, and two deaths were due to sudden cardiac death. Sixty percent of patients treated with cabozantinib had at least one dose reduction while on study. Ten percent of patients in the cabozantinib group required treatment discontinuation and seventy percent required dose modification, including dose interruption or dose

reduction. The most frequent AEs leading to dose reduction of cabozantinib were diarrhea (16%), palmar-plantar erythrodysesthesia syndrome (11%), fatigue (10%), and hypertension (7.6%).
Cabozantinib demonstrated superiority to everolimus with a statistically significant improvement in PFS, OS and ORR. The improvement in median PFS and OS is considered clinically meaningful. Cabozantinib has a favorable benefit-risk profile for treatment of adult patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy."
The following table is derived from the clinical and CDTL reviews. I concur with the statements presented.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In 2015, it is estimated that there will be 61,560 cases and 14,080 deaths from RCC in the U.S. In metastatic renal cell carcinoma, depending on the prognostic features at presentation, the 5 years survival rate can be as low as ~ 10%.	Renal cell carcinoma is a serious and life-threatening condition.
Current Treatment Options	• Except for a selected population who can tolerate IL-2 therapy and for those with poor prognostic factors suitable for temsirolimus, the currently acceptable first-line therapy for unresectable or metastatic clear-cell RCC consists of anti-angiogenic therapy, followed an mTOR inhibitor. After progression from first-line anti-angiogenic therapy, the median progression-free survival and overall survival can be as little as 5 and 20 months, respectively.	There are unmet medical needs to improve the overall survival in metastatic RCC (mRCC).
Benefit	• PFS as assessed by IRC in the PITT population demonstrated a statistically significant improvement in median PFS of 7.4 months (95% CI: 5.6, 9.1] in the cabozantinib arm and 3.8 months (95% CI: 3.7, 5.4) in the everolimus arm [HR: 0.58 (95% CI 0.45, 0.74), stratified log-rank p-value <0.0001, per IVRS]. An OS benefit in a second interim analysis was demonstrated with a median OS of 21.4 months (95% CI: 18.7, not estimable) in the cabozantinib arm and 16.5 months (95% CI: 14.7, 18.8) in the everolimus arm (HR: 0.66, 95% CI: 0.53, 0.83; stratified log-rank p-value =0.0003, per IVRS) representing a median difference in OS of 4.9 months.	The OS and PFS results are statistically significant and clinically meaningful.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	The most common (greater than or equal to 20%) adverse reactions included diarrhea, fatigue, nausea, vomiting, constipation, abdominal pain, decreased appetite, hypertension, rash, palmarplantar erythrodysesthesia, weight decreased, and dygeusia. Serious adverse events were reported in 40% of patients. The most common serious adverse events (greater than or equal to 2%) were abdominal pain, pleural effusion, diarrhea, nausea, and anemia. Fifteen deaths were reported within 30 days of the last cabozantinib dose. Eight of the deaths were attributed to progressive disease, five deaths were due to cognitive deterioration, pneumonia, hemorrhage, cardiac failure, and urosepsis respectively, and two deaths were due to sudden cardiac death.	The safety profile of cabozantinib is acceptable for patients with advanced renal cell carcinoma who have progressed after prior anti-angiogenic therapy. The size of the safety database and duration of cabozantinib exposure were sufficient to characterize the safety of cabozantinib in the studied patient population. The safety profile is similar to the previously characterized profile from thyroid cancer studies.
Risk Management	• There is no proposal for a formal Risk management Plan.	Recommendations for safe and effective use of cabozantinib will be reflected in labeling and patient medication guide.

2. Background

Summary of Presubmission/Submission Regulatory Activity

From the CDTL review

- **June 10, 2005-** IND 72,596 submitted.
- **November 29, 2012**- cabozantinib (Cometriq) was approved for the treatment of patients with progressive, metastatic, medullary thyroid cancer (MTC).
- **January 17, 2013**- FDA and the Applicant discussed a proposal regarding a planned registration study in advanced RCC. FDA agreed on the design of Trial XL184-308, including the choice of comparator arm and the use of PFS as the primary endpoint with a robust evaluation of OS as a secondary end point.
- **February 27, 2013-** Protocol XL184-308, A Phase III, Randomized, Controlled Study of Cabozantinib (XL184) vs Everolimus in Patients with Metastatic Renal Cell Carcinoma that is Refractory to or has Progressed after prior VEGFR Tyrosine Kinase Inhibitor Therapy was submitted to the IND.
- **September 13, 2013**- The Applicant discussed with FDA a tablet formulation of cabozantinib.
- **April 8, 2015**- Fast Track Designation was granted for treatment of patients with advanced renal cell carcinoma who have received one prior therapy.
- **August 21, 2015**- Breakthrough Therapy Designation was granted based on preliminary evidence from Trial XL184-308 which indicated that the treatment effect of cabozantinib may represent a substantial improvement over existing therapies for the treatment of advanced renal cell carcinoma after prior VEGFR-TKI therapy.
- **September 2, 2015**- FDA stated that a review of additional OS analysis would occur during the NDA review. The Applicant stated that additional PK reports would be submitted after the initial filing. FDA also stated that a 120-Day Safety update was not required, and recommended a rolling NDA submission.
- **October 13, 2015**- Rolling NDA submission initiated for the treatment of patients with metastatic RCC after prior VEGFR TKI therapy.
- **December 22, 2015**- final NDA component (Clinical) of the rolling NDA submission was submitted.

Intended Population

From the CDTL Review:

Pathophysiology of Condition

Renal cell carcinoma is a serious and life-threatening condition. In 2015, it is estimated that there will be 61,560 new cases and 14,080 deaths from RCC in the U.S (SEER Stat Fact Sheets: Kidney and Renal Pelvis Cancer 2015). Advanced RCC is most commonly treated with anti-angiogenic therapy in the first line setting, and after progression, the median PFS and OS can be as little as 5 and 20 months, respectively (Drugs@FDA: affinitor USPI and everolimus USPI). There is an unmet medical need to improve clinical outcomes in advanced RCC.

Existing (or Available) Therapies

There are three currently approved therapies for advanced RCC in the second line setting: everolimus, axitinib, and nivolumab. Everolimus is a mTOR inhibitor which demonstrated a median PFS improvement over placebo of 4.9 vs. 1.9 months. Axitinib a tyrosine kinase inhibitor demonstrated a median PFS improvement over sorafenib of 6.7 vs. 4.7 months. Nivolumab, an immunotherapy was approved in 2015 with an median OS benefit over everolimus of 25 vs. 19.6 months.

Product Information

Cabozantinib is an orally bioavailable multi-targeted kinase inhibitor with activity against MET (hepatocyte growth factor receptor protein) and VEGFR2 (vascular endothelial growth factor receptor), as well as other receptors that have been implicated in tumor pathobiology, including AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2.

3. Product Quality

I agree with the clinical CMC reviewers (Xing Wang Ph.D.), Application Technical Lead (Xiao Chen, Ph.D.), and Branch Chief (Anamitro Banerjee Ph.D.) who recommended approval. Adequate data were provided for the manufacture and controls of the drug substance and drug product. The Office of Compliance issued an overall "acceptable" recommendation for all facilities used for manufacturing and control of the drug substance. Although cabozantinib had been previously approved in a capsule formulation for metastatic MTC, the current NDA was for a cabozantinib tablet formulation which will be commercialized under a different trade name and with a different indication. As NDA 208692 is for a new dosage form of an active ingredient that has been approved or marketed in the United States in a different dosage form, the NDA is a Type 3 NDA and not deemed a supplemental application. For further details, refer to the CMC review.

4. Nonclinical Pharmacology/Toxicology

I agree with the nonclinical pharmacology/toxicology reviewer, Elias Zahalka Ph.D., and the team leader, Todd Palmby, Ph.D., who state that there are no outstanding nonclinical pharmacology/toxicology issues that preclude approval and that no additional nonclinical pharmacology/toxicology studies are needed.

5. Clinical Pharmacology

I agree with The clinical pharmacology/pharmacometrics reviewers (Pengfei Song, Ph.D. and Chao Liu, Ph.D.) and team leaders (Qi Liu, Ph.D. and Jingyu Yu Ph.D.), concluded that there are no outstanding clinical pharmacology issues that preclude approval. One clinical pharmacology Postmarketing Commitment (PMC) was agreed to with the applicant. The following information is taken from the Clinical Pharmacology reviews and the agreed upon package insert:

"The proposed dosing regimen of 60 mg cabozantinib oral tablet QD is acceptable from a clinical pharmacology perspective.

Cabozantinib treatment with 60 mg QD oral tablet significantly improved progression-free survival (7.4 months vs 3.8 month) and overall survival (21.4 months vs 16.5 months), as well as objective response rate (17% vs 3%) over everolimus control arm in a randomized Phase 3 trial (Study XL184-308).

Exposure-response analyses support the dose selection of 60 mg QD. Doses higher than 60 mg QD are not considered, given that dose reductions are needed in 60% patients at 60 mg QD. Simulation suggested that lower starting doses such as 40 mg or 20 mg QD likely compromise efficacy though the incidence of dose reductions may be lower than 60 mg QD dose.

The results of hepatic impairment trial (Study XL184-003) suggested after a single oral administration of a 60 mg cabozantinib in capsule form, the geometric LSM ratios for exposure ($AUC_{0\text{-}inf}$) were increased by approximately 81% and 63% in subjects with mild and moderate hepatic impairment, respectively, relative to matched controls. C_{max} values were not markedly different in mild and moderate hepatic impairment relative to matched controls (119% and 103%, respectively).

PMR fulfillment: The fulfillment of this PMR trial has been concluded under NDA203756.

Labeling recommendation: To recommend 40 mg QD as the starting dose in patients with mild or moderate hepatic impairment.

The Labeling language for MTC indication stated that no dose adjustment is recommended in patients with mild to moderate renal impairment based on population PK analysis. In the current submission for RCC, results of a dedicated renal impairment study suggested that C_{max} and AUC values were 19% and 30% higher, respectively, for subjects with mild renal impairment compared to subjects with normal renal function. However, both C_{max} and AUC values were similar between the moderate impairment and control cohorts, with a less than 7% difference in exposure parameters.
Labeling recommendation: No dose adjustment is needed for patients with mild to moderate renal impairment.

Co-administration of multiple doses of esomeprazole (40 mg QD) with a single 100 mg dose of cabozantinib did not decrease cabozantinib plasma exposure. The 90% CIs for the ln-transformed ratio of the test to reference treatment for both AUC_{0-t} and AUC_{0-inf} were within the limits of 80% - 125%. PMR fulfillment: The PMR issued under NDA203756 has been fulfilled (as documented under NDA203756)."

Division Director Comments:
*This application relied heavily on the review performed by the Clinical Pharmacology and Pharmacometrics team. As noted in the clinical pharmacology review: "*Following a single 140 mg dose administration of cabozantinib tablet and capsule formulations, the extent of exposure (AUC_{0-t} and AUC_{0-inf}) was similar for both formulations, with the 90% CIs of the geometric least square mean ratio within 80.00% - 125.00% criteria. However, for C_{max}, the upper limit of the 90% CI around the ratio of LS means (131.65%) was outside the 80.00% -125.00% criteria. Therefore, the systemic exposure following cabozantinib capsule and tablet formulations are similar, though bioequivalence could not be concluded due to small excursion of C_{max} beyond 125% criterion.

Similar steady-state exposures ($C_{trough,ss}$) were observed at different doses across patient populations of medullary thyroid cancer (MTC, 140 mg capsules), advanced renal cell carcinoma (RCC, 60 mg tablet), and castration resistant prostate cancer (CRPC, 60 mg tablet). Correspondingly, the apparent oral clearance predicted by population PK model is 4.4 L/hr in MTC and 2.2 L/hr in RCC. This result is unexpected, as $C_{trough,ss}$ in MTC patients with 140 mg dose is expected to be higher than in RCC patients with 60 mg dose, given similar exposure (C_{max} and AUC) of capsule and tablet formulations after a single dose of 140 mg."

Although the single dose of administration of 140 mg of both the tablet and capsule formulations resulted in similar exposures, the PK data across patient populations indicate that similar exposures were also seen with the 140 mg tablet as compared to the 60 mg capsule formulation. One would intuitively expect that the reduction in dose would result in lower exposures; however, this was not apparent. There is wide variability in exposure that may be linked to the poor solubility of the compound. This variability in exposure and promiscuity of the drug across the kinome, coupled with a long half-life (99 hours) and approximate time to steady-state concentration (15 days) renders this drug poorly suitable for up-titration strategies (start at a lower dose and escalate if the drug is tolerable). Furthermore, the tumor modeling and simulations with reduced starting doses appear to suggest that anti-tumor activity may be compromised with lower starting doses. An in-depth discussion was held with the sponsor regarding the feasibility of a dose-finding study; however, with the available data on hand regarding the pharmacokinetic properties of the tablet formulation, it was decided not to pursue further formal dose-finding strategies, but the applicant has committed to a cross-disease analysis to evaluate the impact of patient population, drug formulation, and doses on the pharmacokinetic properties of cabozantinib. Unfortunately, the strategy of introducing a fixed dose that requires a large proportion of dose reductions and interruptions is familiar to patients and prescribers of other kinase inhibitors and the overall tolerability of this class of agents, especially with the promiscuous kinase inhibitors, remains a problem. Further work is needed as a field to institute better dose optimization strategies.

6. Clinical Microbiology

I agree with the microbiology review by Ying Zhang, Ph.D. which concluded that there were no outstanding microbiology issues that preclude approval and no additional studies were needed.

7. Clinical/Statistical-Efficacy

This efficacy supplement is supported by a single, well-controlled, randomized, multicenter, multinational trial (Trial XL184-308) conducted in 821 patients with advanced RCC who have received prior anti-angiogenic therapy regimens. The following is excerpted from the clinical studies section (14) of the agreed upon text in the cabozantinib (CABOMETYX) package insert regarding the design and efficacy results of Trial XL184-308:

> Study 1 was a randomized (1:1), open-label, multicenter study of CABOMETYX versus everolimus conducted in patients with advanced RCC who had received at least 1 prior anti-angiogenic therapy. Patients had to have a Karnofsky Performance Score (KPS) ≥ 70%. Patients were stratified by the number of prior VEGFR tyrosine kinase inhibitors and Memorial Sloan Kettering Cancer Center (MSKCC) Risk Group.
>
> Patients (N=658) were randomized to receive CABOMETYX (N=330) administered orally at 60 mg daily or everolimus (N=328) administered orally at 10 mg daily. The majority of the patients were male (75%), with a median age of 62 years. Sixty-nine percent (69%) received only one prior anti-angiogenic therapy. Patient distribution by MSKCC risk groups was 46% favorable (0 risk factors), 42% intermediate (1 risk factor), and 13% poor (2 or 3 risk factors). Fifty-four percent (54%) of patients had 3 or more organs with metastatic disease, including lung (63%), lymph nodes (62%), liver (29%), and bone (22%).
>
> The main efficacy outcome measure was progression-free survival (PFS) assessed by a blinded independent radiology review committee among the first 375 subjects randomized. Other efficacy endpoints were objective response rate (ORR) and overall survival (OS) in the Intent-to-Treat (ITT) population. Tumor assessments were conducted every 8 weeks for the first 12 months, then every 12 weeks thereafter. Patients received treatment until disease progression or experiencing unacceptable toxicity. Patients on both arms who had disease progression could continue treatment at the discretion of the investigator.
>
> Statistically significant improvements in PFS, OS, and ORR were demonstrated for CABOMETYX compared to everolimus (Figures 1 and 2 and Tables 4 and 5).

Figure 1: Progression-Free Survival in Study 1 (First 375 Randomized)

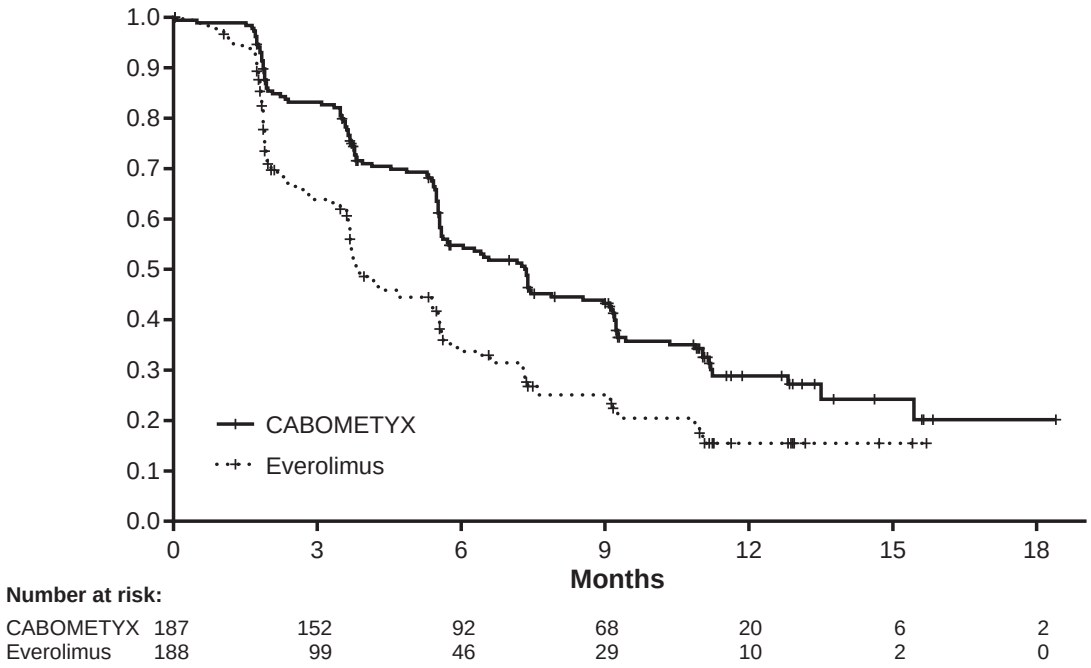

Table 4: Progression-Free Survival in Study 1 (First 375 Randomized)

Endpoint	CABOMETYX	Everolimus
	N = 187	N = 188
Median PFS (95% CI), months	7.4 (5.6, 9.1)	3.8 (3.7, 5.4)
HR (95% CI), p-value[1]	0.58 (0.45, 0.74), p<0.0001	

[1] stratified log-rank test with prior VEGFR-targeting TKI therapy (1 vs 2 or more) and MSKCC prognostic criteria for previously treated patients with RCC (0 vs 1 vs 2 or 3) as stratification factors (per IVRS data)

Figure 2: Overall Survival in Study 1 (ITT)

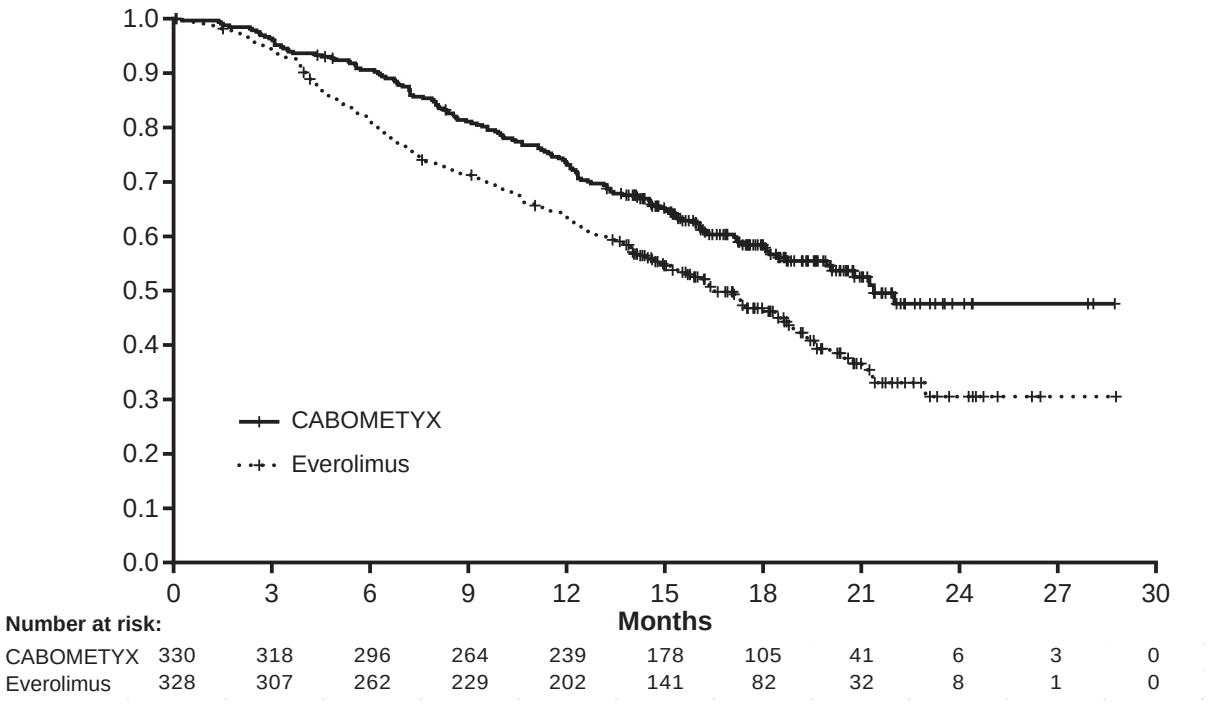

Table 5. Overall Survival and Objective Response Rate in Study 1 (ITT)

Endpoint	CABOMETYX	Everolimus
	N = 330	N = 328
Median OS (95% CI), months	21.4 (18.7, NE)	16.5 (14.7, 18.8)
HR (95% CI), p-value[1]	0.66 (0.53, 0.83), p=0.0003	
Confirmed ORR (partial responses only) (95% CI)	17% (13%, 22%)	3% (2%, 6%)
p-value[2]	p<0.0001	

[1] stratified log-rank test with prior VEGFR-targeting TKI therapy (1 vs 2 or more) and MSKCC prognostic criteria for previously treated patients with RCC (0 vs 1 vs 2 or 3) as stratification factors (per IVRS data)
[2] chi-squared test

8. Safety

The safety results from this trial are summarized below in the following excerpt from section 6.1 of the agreed-upon package insert.

The safety of CABOMETYX was evaluated in Study 1, a randomized, open-label trial in which 331 patients with advanced renal cell carcinoma received 60 mg CABOMETYX and 322 patients received 10 mg everolimus administered daily until disease progression or unacceptable toxicity. Patients on both arms who had disease progression could continue treatment at the discretion of the investigator *[see Clinical Studies (14)]*. The median duration of treatment was 7.6 months (range 0.3 – 20.5) for patients receiving CABOMETYX and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus.

Adverse reactions which occurred in ≥ 25% of CABOMETYX-treated patients included, in order of decreasing frequency: diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia syndrome (PPES), hypertension, vomiting, weight decreased, and constipation. Grade 3-4 adverse reactions and laboratory abnormalities which occurred in ≥ 5% of patients were hypertension, diarrhea, fatigue, palmar-plantar erythrodysesthesia syndrome, hyponatremia, hypophosphatemia, hypomagnesemia, lymphocytes decreased, anemia, hypokalemia, and GGT increased.

The dose was reduced in 60% of patients receiving CABOMETYX and in 24% of patients receiving everolimus. Twenty percent (20%) of patients received 20 mg CABOMETYX as their lowest dose. The most frequent adverse reactions leading to dose reduction in patients treated with CABOMETYX were: diarrhea, PPES, fatigue, and hypertension. Adverse reactions led to study treatment being held in 70% patients receiving CABOMETYX and in 59% patients receiving everolimus. Adverse reactions led to study treatment discontinuation in 10% of patients receiving CABOMETYX and in 10% of patients receiving everolimus. The most frequent adverse reactions leading to permanent discontinuation in patients treated with CABOMETYX were decreased appetite (2%) and fatigue (1%).

Table 1. Adverse Reactions Occurring in ≥ 10% Patients Who Received CABOMETYX

Adverse Reaction	CABOMETYX (n=331) [1]		Everolimus (n=322)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Gastrointestinal Disorders				
Diarrhea	74	11	28	2
Nausea	50	4	28	<1
Vomiting	32	2	14	<1
Stomatitis	22	2	24	2
Constipation	25	<1	19	<1
Abdominal pain [3]	23	4	13	2
Dyspepsia	12	<1	5	0
General Disorders and Administration Site Conditions				
Fatigue	56	9	47	7
Mucosal inflammation	19	<1	23	3
Asthenia	19	4	16	2
Metabolism and Nutrition Disorders				
Decreased appetite	46	3	34	<1
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysesthesia syndrome	42	8	6	<1
Rash [4]	23	<1	43	<1
Dry skin	11	0	10	0
Vascular Disorders				

Hypertension [5]	39	16	8	3
Investigations				
Weight decreased	31	2	12	0
Nervous System Disorders				
Dysgeusia	24	0	9	0
Headache	11	<1	12	<1
Dizziness	11	0	7	0
Endocrine Disorders				
Hypothyroidism	21	0	<1	<1
Respiratory, Thoracic, and Mediastinal Disorders				
Dysphonia	20	<1	4	0
Dyspnea	19	3	29	4
Cough	18	<1	33	<1
Blood and Lymphatic Disorders				
Anemia	17	5	38	16
Musculoskeletal and Connective Tissue Disorders				
Pain in extremity	14	1	8	<1
Muscle spasms	13	0	5	0
Arthralgia	11	<1	14	1
Renal and Urinary Disorders				
Proteinuria	12	2	9	<1

[1] One subject randomized to everolimus received cabozantinib.
[2] National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0
[3] Includes PT terms abdominal pain, abdominal pain upper, and abdominal pain lower
[4] Includes PT terms rash, rash erythematous, rash follicular, rash macular, rash papular, rash pustular, rash vesicular, genital rash, intermittent leg rash, rash on scrotum and penis, rash maculo-papular, rash pruritic, contact dermatitis, dermatitis acneiform
[5] Includes PT terms hypertension, blood pressure increased, hypertensive crisis, blood pressure fluctuation

Other clinically important adverse reactions (all grades) that were reported in <10% of patients treated with CABOMETYX included: wound complications (2%), convulsion (<1%), pancreatitis (<1%), osteonecrosis of the jaw (<1%), and hepatitis cholestatic (<1%).

Table 2. Laboratory Abnormalities Occurring in ≥ 25% Patients Who Received CABOMETYX

Test	CABOMETYX (n=331)		Everolimus (n=322)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Chemistry				
AST increased	74	3	40	<1
ALT increased	68	3	32	<1
Creatinine increased	58	<1	71	0
Triglycerides increased	53	4	73	13
Hypophosphatemia	48	8	36	5
Hyperglycemia	37	2	59	8
Hypoalbuminemia	36	2	28	<1
ALP increased	35	2	29	1
Hypomagnesemia	31	7	4	<1
Hyponatremia	30	8	26	6
GGT increased	27	5	43	9
Hematology				

White blood cells decreased	35	<1	31	<1
Absolute neutrophil count decreased	31	2	17	<1
Hemoglobin decreased	31	4	71	17
Lymphocytes decreased	25	7	39	12
Platelets decreased	25	<1	27	<1
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase. National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0				

The following Warnings and Precautions were included in the Package Insert:

5.1 Hemorrhage

Severe hemorrhage occurred with CABOMETYX. The incidence of Grade ≥ 3 hemorrhagic events was 2.1% in CABOMETYX-treated patients and 1.6% in everolimus-treated patients. Fatal hemorrhages also occurred in the cabozantinib clinical program.

Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage.

5.2 GI Perforations and Fistulas

In a randomized study in renal cell carcinoma, fistulas were reported in 1.2% (including 0.6% anal fistula) of CABOMETYX-treated patients and 0% of everolimus-treated patients. Gastrointestinal (GI) perforations were reported in 0.9% of CABOMETYX-treated patients and 0.6% of everolimus-treated patients. Fatal perforations occurred in the cabozantinib clinical program.

Monitor patients for symptoms of fistulas and perforations. Discontinue CABOMETYX in patients who experience a fistula which cannot be appropriately managed or a GI perforation.

5.3 Thrombotic Events

CABOMETYX treatment results in an increased incidence of thrombotic events. Venous thromboembolism was reported in 7.3% of CABOMETYX-treated patients and 2.5% of everolimus-treated patients. Pulmonary embolism occurred in 3.9% of CABOMETYX-treated patients and 0.3% of everolimus-treated patients. Events of arterial thromboembolism were reported in 0.9% of CABOMETYX-treated patients and 0.3% of everolimus-treated patients. Fatal thrombotic events occurred in the cabozantinib clinical program.

Discontinue CABOMETYX in patients who develop an acute myocardial infarction or any other arterial thromboembolic complication.

5.4 Hypertension and Hypertensive Crisis

CABOMETYX treatment results in an increased incidence of treatment-emergent hypertension. Hypertension was reported in 37% (15% Grade ≥ 3) of CABOMETYX-treated patients and 7.1% (3.1% Grade ≥ 3) of everolimus-treated patients. Monitor blood pressure prior to initiation and regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy. Discontinue CABOMETYX if there is evidence of hypertensive crisis or severe hypertension despite optimal medical management.

5.5 Diarrhea

Diarrhea occurred in 74% of patients treated with CABOMETYX and in 28% of patients treated with everolimus. Grade 3 diarrhea occurred in 11% of CABOMETYX-treated patients and in 2% of everolimus-treated patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 diarrhea or Grade 3-4 diarrhea that cannot be managed with standard antidiarrheal treatments until improvement to Grade 1; resume CABOMETYX at a reduced dose. Dose modification due to diarrhea occurred in 26% of patients.

5.6 Palmar-Plantar Erythrodysesthesia Syndrome

Palmar-plantar erythrodysesthesia syndrome (PPES) occurred in 42% of patients treated with CABOMETYX and in 6% of patients treated with everolimus. Grade 3 PPES occurred in 8.2% of CABOMETYX-treated patients and in <1% of everolimus-treated patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPES or Grade 3 PPES until improvement to Grade 1; resume CABOMETYX at a reduced dose. Dose modification due to PPES occurred in 16% of patients.

5.7 Reversible Posterior Leukoencephalopathy Syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in the cabozantinib clinical program. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

5.8 Embryo-fetal Toxicity

Based on data from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. Cabozantinib administration to pregnant animals during organogenesis resulted in embryolethality at exposures below those occurring clinically at the recommended dose, and in increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the last dose *[See Use in Specific Populations (8.1), (8.3), and Clinical Pharmacology (12.1)]*.

9. Advisory Committee Meeting

This efficacy supplement was not referred to a meeting of the Oncologic Drugs Advisory Committee.

10. Pediatrics

A pediatric waiver was granted by the PeRC.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

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

12. Labeling

Agreement has been reached on the physician labeling. The final indication is for the treatment of patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy.

The efficacy (14) and safety (5, 6.1) sections of the package insert are discussed in prior sections of this review.

13. Postmarketing

There was no recommendation for Postmarketing Risk Evaluation and Mitigation Strategies.

The applicant has agreed to the following post marketing commitment as discussed in a previous section of this review:

3063-1 Combine all available pharmacokinetics (PK) data from different patient populations and healthy subjects in an integrated population PK model to evaluate the potential impact of tumor types on the PK of cabozantinib.

Final Report Submission: 06/16

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

/s/

GEOFFREY S KIM
04/25/2016