



## Exelixis Submits U.S. Supplemental New Drug Application for CABOMETRYX® (cabozantinib) for the Treatment of Previously Untreated Advanced Kidney Cancer

August 16, 2017

– CABOMETRYX is the first therapy to demonstrate a clinically meaningful and statistically significant progression-free survival benefit over the current standard of care –

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Aug. 16, 2017-- [Exelixis, Inc.](#) (NASDAQ:EXEL) today announced it has completed the submission of a supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) for CABOMETRYX® (cabozantinib) tablets as a treatment for patients with previously untreated advanced renal cell carcinoma (RCC). The sNDA submission is based on results from the CABOSUN randomized phase 2 trial of CABOMETRYX in patients with previously untreated advanced RCC with intermediate- or poor-risk disease per the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC).

"All of us at Exelixis are focused on improving care and outcomes for patients with cancer. Having successfully launched CABOMETRYX for patients with previously treated advanced RCC, the submission of this sNDA for CABOMETRYX as a treatment in the first-line RCC setting represents an important milestone for us," said Michael M. Morrissey, Ph.D., President and Chief Executive Officer of Exelixis. "If approved, CABOMETRYX will offer an important new alternative for the treatment of patients with previously untreated advanced RCC, having demonstrated a clinically meaningful and statistically significant progression-free survival benefit over sunitinib, a current standard of care. We would like to sincerely thank the study patients and clinicians who participated in the CABOSUN trial, the Alliance and NCI-CTEP, as well as our dedicated clinical, medical and regulatory teams for bringing us one step closer to our goal of expanding the population of patients who may benefit from CABOMETRYX."

CABOSUN was conducted by The Alliance for Clinical Trials in Oncology as part of Exelixis' collaboration with the National Cancer Institute's Cancer Therapy Evaluation Program (NCI-CTEP). On May 23, 2016, Exelixis announced that CABOSUN met its primary endpoint, demonstrating a clinically meaningful and statistically significant improvement in progression-free survival (PFS) compared with sunitinib in patients with advanced intermediate- or poor-risk RCC as determined by investigator assessment. These results were first presented by Dr. Toni Choueiri at the meeting of the European Society for Medical Oncology 2016, and published in the *Journal of Clinical Oncology* (Choueiri, *JCO*, 2016).<sup>1</sup> In June 2017, Exelixis announced that the analysis of the review by a blinded independent radiology review committee (IRC) confirmed the primary efficacy endpoint results of investigator-assessed PFS from the CABOSUN trial.

An sNDA is an application to the FDA that, if approved, will allow a drug sponsor to make changes to a previously approved product label, including modifications to the indication. CABOMETRYX was previously approved by the FDA on April 25, 2016 for the treatment of patients with advanced RCC who have received prior anti-angiogenic therapy. The approval was based on results from the phase 3 METEOR trial, which demonstrated that CABOMETRYX provided a statistically significant and clinically meaningful improvement in overall survival, PFS and objective response rate as compared with everolimus in this patient population.

### About the CABOSUN Study

CABOSUN was a randomized, open-label, active-controlled phase 2 trial that enrolled 157 patients with advanced RCC determined to be intermediate- or poor-risk by the IMDC criteria. Patients were randomized 1:1 to receive cabozantinib (60 mg once daily) or sunitinib (50 mg once daily, 4 weeks on followed by 2 weeks off). The primary endpoint was PFS. Secondary endpoints included overall survival and objective response rate. Eligible patients were required to have locally advanced or metastatic clear-cell RCC, ECOG performance status 0-2 and had to be intermediate or poor risk per the IMDC criteria (Heng, *JCO*, 2009).<sup>2</sup> Prior systemic treatment for RCC was not permitted.

Please see Important Safety Information below and full U.S. prescribing information at <https://cabometryx.com/downloads/cabometryxuspi.pdf>.

### About Advanced Renal Cell Carcinoma

The American Cancer Society's 2017 statistics cite kidney cancer as among the top ten most commonly diagnosed forms of cancer among both men and women in the U.S.<sup>3</sup> Clear cell RCC is the most common type of kidney cancer in adults.<sup>4</sup> If detected in its early stages, the five-year survival rate for RCC is high; for patients with advanced or late-stage metastatic RCC, however, the five-year survival rate is only 12 percent, with no identified cure for the disease.<sup>5</sup> Approximately 30,000 patients in the U.S. and 68,000 globally require treatment, and an estimated 14,000 patients in the U.S. each year are in need of a first-line treatment for advanced kidney cancer.<sup>6</sup>

The majority of clear cell RCC tumors have lower than normal levels of a protein called von Hippel-Lindau, which leads to higher levels of MET, AXL and VEGF.<sup>7,8</sup> These proteins promote tumor angiogenesis (blood vessel growth), growth, invasiveness and metastasis.<sup>9-12</sup> MET and AXL may provide escape pathways that drive resistance to VEGF receptor inhibitors.<sup>7,8</sup>

### About CABOMETRYX® (cabozantinib)

CABOMETRYX is the tablet formulation of cabozantinib. Its targets include MET, AXL and VEGFR-1, -2 and -3. In preclinical models, cabozantinib has been shown to inhibit the activity of these receptors, which are involved in normal cellular function and pathologic processes such as tumor angiogenesis, invasiveness, metastasis and drug resistance.

CABOMETRYX is available in 20 mg, 40 mg or 60 mg doses. The recommended dose is 60 mg orally, once daily.

On April 25, 2016, the FDA approved CABOMETRYX tablets for the treatment of patients with advanced RCC who have received prior anti-angiogenic therapy. In February of 2016, Exelixis and Ipsen jointly announced an exclusive licensing agreement for the commercialization and further development of cabozantinib indications outside of the United States, Canada and Japan. This agreement was amended in December of 2016 to

include commercialization rights for Ipsen in Canada. On September 9, 2016, the European Commission approved CABOMETYX tablets for the treatment of advanced RCC in adults who have received prior vascular endothelial growth factor (VEGF)-targeted therapy in the European Union, Norway and Iceland. Ipsen has confirmed its intent to submit the regulatory dossier for cabozantinib as a treatment for first-line advanced RCC in the European Union in the third quarter of 2017.

On January 30, 2017, Exelixis and Takeda Pharmaceutical Company Limited announced an exclusive licensing agreement for the commercialization and further clinical development of cabozantinib for all future indications in Japan, including RCC.

CABOMETYX is not indicated for the treatment of previously untreated advanced RCC.

### U.S. Important Safety Information

**Hemorrhage:** Severe hemorrhage occurred with CABOMETYX. The incidence of Grade  $\geq 3$  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.

**Gastrointestinal (GI) Perforations and Fistulas:** Fistulas were reported in 1.2% (including 0.6% anal fistula) of CABOMETYX-treated patients and 0% of everolimus-treated patients. 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 that cannot be appropriately managed or a GI perforation.

**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.

**Hypertension and Hypertensive Crisis:** CABOMETYX treatment results in an increased incidence of treatment-emergent hypertension. Hypertension was reported in 37% (15% Grade  $\geq 3$ ) of CABOMETYX-treated patients and 7.1% (3.1% Grade  $\geq 3$ ) 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.

**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.

**Palmar-Plantar Erythrodysesthesia Syndrome (PPES):** 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.

**Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** 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.

**Embryo-fetal Toxicity:** CABOMETYX can cause fetal harm when administered to a pregnant woman. 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.

**Adverse Reactions:** The most commonly reported ( $\geq 25\%$ ) adverse reactions are: diarrhea, fatigue, nausea, decreased appetite, PPES, hypertension, vomiting, weight decreased, and constipation.

**Drug Interactions: Strong CYP3A4 inhibitors and inducers:** Reduce the dosage of CABOMETYX if concomitant use with strong CYP3A4 inhibitors cannot be avoided. Increase the dosage of CABOMETYX if concomitant use with strong CYP3A4 inducers cannot be avoided.

**Lactation:** Advise a lactating woman not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

**Reproductive Potential: Contraception—**Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose. **Infertility —**CABOMETYX may impair fertility in females and males of reproductive potential.

**Hepatic Impairment:** Reduce the CABOMETYX dose in patients with mild (Child-Pugh score [C-P] A) or moderate (C-P B) hepatic impairment. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

Please see full Prescribing Information at <https://cabometyx.com/downloads/cabometyxuspi.pdf>.

### About Exelixis

Exelixis, Inc. (Nasdaq: EXEL) is a biopharmaceutical company committed to the discovery, development and commercialization of new medicines to improve care and outcomes for people with cancer. Since its founding in 1994, three products discovered at Exelixis have progressed through clinical development, received regulatory approval, and entered the marketplace. Two are derived from cabozantinib, an inhibitor of multiple tyrosine kinases including VEGF, MET, AXL and RET receptors: CABOMETYX<sup>®</sup> tablets approved for previously treated advanced renal cell carcinoma and COMETRIQ<sup>®</sup> capsules approved for progressive, metastatic medullary thyroid cancer. The third product, COTELLIC<sup>®</sup>, is a formulation of cobimetinib, a reversible inhibitor of MEK, is marketed under a collaboration with Genentech (a member of the Roche Group), and is approved as part of a combination regimen to treat advanced melanoma. Both cabozantinib and cobimetinib have shown potential in a variety of forms of cancer and are the

subjects of broad clinical development programs. For more information about Exelixis, please visit [www.exelixis.com](http://www.exelixis.com) or follow @ExelixisInc on Twitter.

### Forward-Looking Statement Disclaimer

This press release contains forward-looking statements, including, without limitation, statements related to Exelixis' focus and commitment to the discovery, development and commercialization of new medicines with the potential to improve care and outcomes for people with cancer; the potential of cabozantinib to benefit patients with previously-untreated advanced RCC; Exelixis' focus on further developing cabozantinib and advancing closer to its goal of expanding the population of patients who may benefit from cabozantinib; the intent of Exelixis' partner, Ipsen, to submit the regulatory dossier for cabozantinib as a treatment for first-line advanced RCC in the EU in the third quarter of 2017; and cobimetinib's continued development and its potential in a variety of forms of cancer. Words such as "will," "may," "intends," "committed," "potential," or other similar expressions identify forward-looking statements, but the absence of these words does not necessarily mean that a statement is not forward-looking. In addition, any statements that refer to expectations, projections or other characterizations of future events or circumstances are forward-looking statements. These forward-looking statements are based upon Exelixis' current plans, assumptions, beliefs, expectations, estimates and projections. Forward-looking statements involve risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in the forward-looking statements as a result of these risks and uncertainties, which include, without limitation: the availability of data at the referenced times; risks related to the potential failure of cabozantinib to demonstrate safety and efficacy in clinical testing; risks and uncertainties related to regulatory review and approval processes and Exelixis' compliance with applicable legal and regulatory requirements; Exelixis' dependence on its relationship with Genentech/Roche with respect to cobimetinib and Exelixis' ability to maintain its rights under the collaboration; Exelixis' ability to protect the company's intellectual property rights; market competition; changes in economic and business conditions, and other factors discussed under the caption "Risk Factors" in Exelixis' quarterly report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on May 1, 2017, and in Exelixis' future filings with the SEC. The forward-looking statements made in this press release speak only as of the date of this press release. Exelixis expressly disclaims any duty, obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein to reflect any change in Exelixis' expectations with regard thereto or any change in events, conditions or circumstances on which any such statements are based.

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