



Exelixis Announces U.S. FDA Grants Priority Review for CABOMETYX® (Cabozantinib) as a Treatment for Previously Untreated Advanced Renal Cell Carcinoma

October 16, 2017

– FDA assigns Prescription Drug User Fee Act action date of February 15, 2018 –

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Oct. 16, 2017-- [Exelixis, Inc.](http://www.exelixis.com) (NASDAQ:EXEL) today announced that the U.S. Food and Drug Administration (FDA) has determined the company's supplemental New Drug Application (sNDA) for CABOMETYX® (cabozantinib) for patients with previously untreated advanced renal cell carcinoma (RCC) to be sufficiently complete to permit a substantive review. The FDA granted Priority Review of the filing and assigned a Prescription Drug User Fee Act (PDUFA) action date of February 15, 2018.

"The acceptance of the sNDA filing with a Priority Review is an important regulatory milestone for CABOMETYX and for our mission to improve treatment outcomes for patients with cancer," said Gisela Schwab, M.D., President, Product Development and Medical Affairs and Chief Medical Officer, Exelixis. "We look forward to working with the FDA as they review the application in our effort to offer CABOMETYX to patients with previously untreated metastatic RCC who are in need of new treatment options."

The sNDA is based on data from CABOSUN, a randomized phase 2 trial 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).

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. CABOMETYX 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 CABOMETYX provided a statistically significant and clinically meaningful improvement in overall survival, progression-free survival (PFS), and objective response rate as compared with everolimus in this patient population.

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

About the CABOSUN Study

On May 23, 2016, Exelixis announced that CABOSUN met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in PFS compared with sunitinib in patients with advanced intermediate- or poor-risk RCC as determined by investigator assessment. CABOSUN was conducted by The Alliance for Clinical Trials in Oncology as part of Exelixis' collaboration with the NCI-CTEP. These results were first presented by Dr. Toni Choueiri at the European Society for Medical Oncology (ESMO) 2016 Congress, and published in the *Journal of Clinical Oncology* (Choueiri, *JCO*, 2016).¹ In June 2017, a blinded independent radiology review committee (IRC) confirmed that cabozantinib provided a clinically meaningful and statistically significant improvement in the primary efficacy endpoint of investigator-assessed PFS. Results from the IRC review were presented by Dr. Toni Choueiri at the ESMO 2017 Congress.

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).² Prior systemic treatment for RCC was not permitted.

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.³ Clear cell RCC is the most common type of kidney cancer in adults.⁴ 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.⁵ 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.⁶

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.^{7,8} These proteins promote tumor angiogenesis (blood vessel growth), growth, invasiveness and metastasis.⁹⁻¹² MET and AXL may provide escape pathways that drive resistance to VEGF receptor inhibitors.^{7,8}

About CABOMETYX® (cabozantinib)

CABOMETYX 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. CABOMETYX 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 CABOMETYX 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 also submitted to European Medicines Agency (EMA) the regulatory dossier for cabozantinib as a treatment for first-line advanced RCC in the European Union on August 28, 2017; on September 8, 2017, Ipsen announced that the EMA validated the application.

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 ≥ 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 ≥ 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.

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

Founded in 1994, Exelixis, Inc. (NASDAQ:EXEL) is a commercially successful, oncology-focused biotechnology company that strives to accelerate the discovery, development and commercialization of new medicines for difficult-to-treat cancers. Following early work in model genetic systems, we established a broad drug discovery and development platform that has served as the foundation for our continued efforts to bring new cancer

therapies to patients in need. We discovered our lead compounds, cabozantinib and cobimetinib, and advanced them into clinical development before entering into partnerships with leading biopharmaceutical companies in our efforts to bring them to patients globally. With growing revenues from the three resulting commercialized products – CABOMETYX®, COMETRIQ®, and COTELLIC® – we are reinvesting in our business to maximize the potential of our pipeline, which we intend to supplement with targeted business development activities and internal drug discovery, all to deliver the next generation of Exelixis medicines and help patients recover stronger and live longer. For more information about Exelixis, please visit 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: the impact of the FDA's grant of Priority Review for Exelixis' sNDA for CABOMETYX as a treatment for patients with previously untreated advanced renal cell carcinoma on Exelixis' ability to improve treatment outcomes for patients with cancer; Exelixis' plans to work with the FDA during the regulatory review process; growing revenues from CABOMETYX, COMETRIQ, and COTELLIC and Exelixis' plans to reinvest in its business to maximize the potential of the company's pipeline, including through targeted business development activities and internal drug discovery; and Exelixis' mission to deliver the next generation of Exelixis medicines and help patients recover stronger and live longer. Words such as "mission," "look forward," "potential," "intend," 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: risks and uncertainties related to regulatory review and approval processes and Exelixis' compliance with applicable legal and regulatory requirements; risks related to the potential failure of cabozantinib to demonstrate safety and efficacy in clinical testing; Exelixis' ability to conduct clinical trials of cabozantinib sufficient to achieve a positive completion; Exelixis' dependence on its relationships with its cabozantinib collaboration partners, including, the level of their investment in the resources necessary to successfully commercialize cabozantinib in the territories where it is approved; market acceptance of CABOMETYX, COMETRIQ, and COTELLIC and the availability of coverage and reimbursement for these products; the risk that unanticipated developments could adversely affect the commercialization of CABOMETYX, COMETRIQ, and COTELLIC; the level of costs associated with Exelixis' commercialization, research and development and other activities; Exelixis' dependence on its relationship with Genentech/ Roche with respect to cobimetinib and Exelixis' ability to maintain its rights under the collaboration; Exelixis' dependence on third-party vendors; 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 August 2, 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.

Exelixis, the Exelixis logo, CABOMETYX, COMETRIQ and COTELLIC are registered U.S. trademarks.

References

1. Choueiri, T.K., et al. Cabozantinib versus Sunitinib as Initial Targeted Therapy for Patients with Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. *Am J Clin Oncol*. 2016; 35:591-597.
2. Heng D.Y., Xie W., Regan M.M., et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: Results from a large, multicenter study. *Am J Clin Oncol*. 2009; 27:5794-5799.
3. American Cancer Society. Cancer Facts & Figures 2017. Atlanta: American Cancer Society; 2017.
4. Jonasch, E., Gao, J., Rathmell, W. Renal cell carcinoma. *BMJ*. 2014; 349:g4797.
5. Ko, J., Choueiri, T., et al. First-, second- third-line therapy for mRCC: benchmarks for trial design from the IMDC. *Br J Cancer*. 2014; 110:1917-1922.
6. Decision Resources Report: Renal Cell Carcinoma. October 2014 (internal data on file).
7. Harshman, L., and Choueiri, T. Targeting the hepatocyte growth factor/c-Met signaling pathway in renal cell carcinoma. *Cancer J*. 2013; 19:316-323.
8. Rankin, et al. Direct regulation of GAS6/AXL signaling by HIF promotes renal metastasis through SRC and MET. *Proc Natl Acad Sci U S A*. 2014; 111:13373-13378.
9. Zhou, L., Liu, X-D., Sun, M., et al. Targeting MET and AXL overcomes resistance to sunitinib therapy in renal cell carcinoma. *Oncogene*. 2016; 35:2687-2697.
10. Koochekpour, et al. The von Hippel-Lindau tumor suppressor gene inhibits hepatocyte growth factor/scatter factor-induced invasion and branching morphogenesis in renal carcinoma cells. *Mol Cell Biol*. 1999; 19:5902-5912.
11. Takahashi, A., Sasaki, H., Kim, S., et al. Markedly increased amounts of messenger RNAs for vascular endothelial growth factor and placenta growth factor in renal cell carcinoma associated with angiogenesis. *Cancer Res*. 1994; 54:4233-4237.
12. Nakagawa, M., Emoto, A., Hanada, T., Nasu, N., Nomura, Y. Tubulogenesis by microvascular endothelial cells is mediated by vascular endothelial growth factor (VEGF) in renal cell carcinoma. *Br J Urol*. 1997; 79:681-687.

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