European Commission Approves CABOMETYX™ (cabozantinib) Tablets for the Treatment of Advanced Renal Cell Carcinoma Following VEGF-Targeted Therapy

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– CABOMETYX is the first and only therapy approved in the European Union to demonstrate improved overall survival, progression-free survival and objective response rate in a large, randomized phase 3 trial of patients with advanced kidney cancer –

– Approval of CABOMETYX in European Union triggers $60 million milestone payment to Exelixis under licensing agreement with Ipsen –

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Sep. 14, 2016-- Exelixis, Inc. (NASDAQ:EXEL) today announced that the European Commission (EC) has approved CABOMETYX™ (cabozantinib) tablets for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy. CABOMETYX was granted accelerated assessment by the European Medicines Agency, and is the first therapy to demonstrate in a phase 3 trial for patients with advanced RCC, robust and clinically meaningful improvements in all three key efficacy parameters — overall survival (OS), progression-free survival (PFS) and objective response rate (ORR). This approval allows for the marketing of CABOMETYX in all 28 member states of the European Union, Norway and Iceland.

EC approval of CABOMETYX triggers a $60 million milestone payment to Exelixis under the licensing agreement with Ipsen for the commercialization and further development of CABOMETYX indications outside of the United States, Canada and Japan. The approval is based on the results of the large, randomized phase 3 METEOR trial.

“The marketing authorization of CABOMETYX by the European Commission to treat patients with advanced renal cell carcinoma reflects the strong efficacy results observed with cabozantinib in the phase 3 METEOR trial, and is an important milestone in our collaboration with Ipsen,” said Michael M. Morrissey, Ph.D., president and chief executive officer of Exelixis. “This marketing authorization helps address an unmet medical need in Europe by providing patients with a new therapy that slows disease progression and prolongs overall survival. We look forward to further examining the use of CABOMETYX in earlier lines of therapy and in other difficult-to-treat cancers.”

About CABOMETYX™ (cabozantinib)

CABOMETYX is the tablet formulation of cabozantinib. CABOMETYX 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, the U.S. FDA approved CABOMETYX tablets for the treatment of patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy. On September 9, 2016, the European Commission approved CABOMETYX tablets for the treatment of advanced renal cell carcinoma in adults who have received prior vascular endothelial growth factor (VEGF)-targeted therapy in the European Union, Norway and Iceland.

On February 29, 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.

About the METEOR Phase 3 Pivotal Trial

METEOR was an open-label, event-driven trial of 658 patients with advanced renal cell carcinoma who had failed at least one prior VEGFR TKI therapy. The primary endpoint was PFS in the first 375 patients randomized. Secondary endpoints included OS and objective response rate in all enrolled patients. The trial was conducted at approximately 200 sites in 26 countries, and enrollment was weighted toward Western Europe, North America, and Australia. Patients were randomized 1:1 to receive 60 mg of CABOMETYX daily or 10 mg of everolimus daily and were stratified based on the number of prior VEGFR TKI therapies received and on MSKCC risk criteria. No cross-over was allowed between the study arms.

METEOR met its primary endpoint by significantly improving PFS. Compared with everolimus, CABOMETYX was associated with a 42 percent reduction in the rate of disease progression or death. Median PFS for CABOMETYX was 7.4 months versus 3.8 months for everolimus (HR=0.58, 95% CI 0.45-0.74, P<0.0001). CABOMETYX also significantly improved the objective response rate compared with everolimus, be it through investigator assessment (24% versus 4%, p<0.0001) or through central review (17% versus 3%, p < 0.0001). These data were presented at the European Cancer Congress in September 2015 and published in *The New England Journal of Medicine*.[1]

CABOMETYX also demonstrated a statistically significant and clinically meaningful increase in OS in the METEOR trial. Compared with everolimus, CABOMETYX was associated with a 34 percent reduction in the rate of death. Median OS was 21.4 months for patients receiving CABOMETYX versus 16.5 months for those receiving everolimus (HR=0.66, 95% CI 0.53-0.83, P=0.0003).

CABOMETYX benefit in OS was robust and consistent across all pre-specified subgroups. In particular, benefit was observed regardless of risk category, location and extent of tumor metastases, and tumor MET expression level. These results were presented on June 5, 2016 at the ASCO Annual Meeting and concurrently published in *The Lancet Oncology*.[2]

At the time of the analysis, the median duration of treatment in the trial was 8.3 months with CABOMETYX versus 4.4 months with everolimus. The most frequent adverse events regardless of causality were diarrhea, fatigue, decreased appetite and hypertension for CABOMETYX and fatigue, anemia, decreased appetite and cough for everolimus. Dose reductions occurred for 62 percent and 25 percent of patients, respectively. Discontinuation rate due to an adverse event not related to disease progression was 12 percent with CABOMETYX and 11 percent with everolimus.

About Advanced Renal Cell Carcinoma

Renal cell carcinoma (RCC) represents 2-3 percent of all cancers[3], with the highest incidence occurring in Western countries. Generally, during the last two decades until recently, there has been an annual increase of about 2 percent in incidence both worldwide and in Europe, though in Denmark and Sweden a continuing decrease has been observed.[4] In 2012, there were approximately 84,400 new cases of RCC and 34,700 kidney cancer related deaths within the European Union.[5] In Europe, overall mortality rates for RCC have increased up until the early 1990s, with rates generally stabilizing or declining thereafter.[6] There has been a decrease in mortality since the 1980s in Scandinavian countries and since the early 1990s in France, Germany, Austria, the Netherlands, and Italy. However, in some European countries (Croatia, Estonia, Greece, Ireland, Slovakia), mortality rates still show an upward trend with increasing rates. [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 VEGFR inhibitors.[8,9]

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 (≥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 with the potential to improve care and outcomes for people with cancer. Since its founding in 1994, three medicines discovered at Exelixis have progressed through clinical development to receive regulatory approval. Currently, Exelixis is focused on advancing cabozantinib, an inhibitor of multiple tyrosine kinases including MET, AXL and VEGF receptors, which has shown clinical anti-tumor activity in more than 20 forms of cancer and is the subject of a broad clinical development program. Two separate formulations of cabozantinib have received regulatory approval to treat certain forms of kidney and thyroid cancer and are marketed for those purposes as CABOMETYX™ tablets (U.S. and EU) and COMETRIQ® capsules (U.S. and EU), respectively. Another Exelixis-discovered compound, COTELLIC™ (cobimetinib), a selective inhibitor of MEK, has been approved in major territories including the United States and European Union, and is being evaluated for further potential indications by Roche and Genentech (a member of the Roche Group) under a collaboration with Exelixis. For more information on 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: Exelixis' further examination of the use of CABOMETYX in earlier lines of therapy and in other difficult-to-treat cancers; Exelixis' commitment to the discovery, development and commercialization of new medicines with the potential to improve care and outcomes for people with cancer; Exelixis' focus on advancing cabozantinib; and the continued development of cobimetinib. Words such as "look forward," "committed," "focused," "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 degree of market acceptance of CABOMETYX and the availability of coverage and reimbursement for CABOMETYX; the risk that unanticipated developments could adversely affect the commercialization of CABOMETYX; Exelixis' dependence on its relationship with Ipsen, including, the level of Ipsen's investment in the resources necessary to successfully commercialize cabozantinib in the territories where it is approved; risks and uncertainties related to regulatory review and approval processes and Exelixis' compliance with applicable legal and regulatory requirements; Exelixis' ability to conduct clinical trials of cabozantinib sufficient to achieve a positive completion; risks related to the potential failure of cabozantinib to demonstrate safety and efficacy in clinical testing; 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 3, 2016, 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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