Exelixis' Partner Ipsen Announces EMA Validation of the Application for a New Indication for CABOMETYX® (cabozantinib) for Previously Treated Advanced Hepatocellular Carcinoma

March 28, 2018

– In the pivotal phase 3 CELESTIAL trial, CABOMETYX provided a statistically significant and clinically meaningful improvement versus placebo in overall survival –

– Exelixis announced the completed submission of a supplemental New Drug Application to the U.S. Food and Drug Administration for CABOMETYX for previously treated patients with advanced hepatocellular carcinoma on March 15 –

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Mar. 28, 2018-- Exelixis, Inc. (NASDAQ:EXEL) today announced that its partner Ipsen received validation of the application for variation to the CABOMETYX® (cabozantinib) marketing authorization from the European Medicines Agency (EMA), the European regulatory authority, for the addition of a new indication for patients with previously treated advanced hepatocellular carcinoma (HCC). The filing is based on results of the global pivotal phase 3 CELESTIAL trial, which met its primary endpoint of overall survival (OS), with cabozantinib providing a statistically significant and clinically meaningful improvement in OS compared with placebo in patients with advanced HCC who had been previously treated with sorafenib (pre-specified critical p-value ≤ 0.021).

"We are excited by the potential benefit CABOMETYX may offer patients in the European Union diagnosed with previously treated advanced hepatocellular carcinoma, a patient community that has very limited treatment options," said Michael M. Morrissey, Ph.D., President and Chief Executive Officer of Exelixis. "This milestone represents significant progress in our collaboration and development program with Ipsen to expand the use of CABOMETYX to additional patient populations outside of the currently approved indication."

Under the terms of the Collaboration and License Agreement with Ipsen, upon the acceptance of this filing, Exelixis earned a $10 million milestone payment. Due to new revenue recognition standards the company adopted in the first quarter of 2018, Exelixis will not record this amount as revenue but expects the milestone to be paid by Ipsen in the second quarter of this year.

On March 6, 2017, the U.S. Food and Drug Administration (FDA) granted orphan drug designation to cabozantinib for the treatment of advanced HCC. On October 16, 2017, Exelixis announced that the independent data monitoring committee for the CELESTIAL study recommended that the trial be stopped for efficacy following review at the second planned interim analysis.

On March 15, 2018, Exelixis announced the completed submission of a supplemental New Drug Application (sNDA) to the FDA for CABOMETYX for previously treated advanced HCC based on findings from CELESTIAL. 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.

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

About the CELESTIAL Study

CELESTIAL is a randomized, double-blind, placebo-controlled study of cabozantinib in patients with advanced HCC conducted at more than 100 sites globally in 19 countries. The trial was designed to enroll 760 patients with advanced HCC who received prior sorafenib and may have received up to two prior systemic cancer therapies for HCC and had adequate liver function. Enrollment of the trial was completed in September 2017. Patients were randomized 2:1 to receive 60 mg of cabozantinib once daily or placebo and were stratified based on etiology of the disease (hepatitis C, hepatitis B or other), geographic region (Asia versus other regions) and presence of extrahepatic spread and/or macrovascular invasion (yes or no). No cross-over was allowed between the study arms during the blinded treatment phase of the trial. The primary endpoint for the trial is OS, and secondary endpoints include objective response rate and progression-free survival. Exploratory endpoints include patient-reported outcomes, biomarkers and safety.

About HCC

Liver cancer is the second-leading cause of cancer death worldwide, accounting for more than 700,000 deaths and nearly 800,000 new cases each year.[1] In the U.S., the incidence of liver cancer has more than tripled since 1980.[2] HCC is the most common form of liver cancer, making up about three-fourths of the estimated nearly 42,000 new cases in the U.S. in 2018.[2] HCC is the fastest-rising cause of cancer-related death in U.S.[3] Without treatment, patients with advanced HCC usually survive less than 6 months.[4]

About CABOMETYX® (cabozantinib)

CABOMETYX tablets are approved in the United States for the treatment of patients with advanced renal cell carcinoma (RCC). CABOMETYX tablets are also approved in the European Union, Norway, Iceland, Australia, Switzerland and South Korea for the treatment of advanced RCC in adults who have received prior vascular endothelial growth factor (VEGF)-targeted therapy. Ipsen also submitted to the EMA the regulatory dossier for cabozantinib as a treatment for first-line advanced RCC in the European Union on August 28, 2017; on March 23, 2018, the CHMP provided a positive opinion for CABOMETYX for the first-line treatment of intermediate- or poor-risk advanced RCC. In 2016, Exelixis granted Ipsen exclusive rights for the commercialization and further clinical development of cabozantinib outside of the United States and Japan. In 2017, Exelixis granted exclusive rights to Takeda Pharmaceutical Company Limited for the commercialization and further clinical development of cabozantinib for all future indications in Japan, including RCC.

CABOMETYX is not indicated for previously treated advanced HCC.

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

U.S. Important Safety Information

- **Hemorrhage**: Severe and fatal hemorrhages have occurred with CABOMETYX. In two RCC studies, the incidence of Grade ≥ 3 hemorrhagic events was 3% in CABOMETYX-treated patients. Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage.
- **Gastrointestinal (GI) Perforations and Fistulas:** In RCC studies, fistulas were reported in 1% of CABOMETYX-treated patients. Fatal perforations occurred in patients treated with CABOMETYX. In RCC studies, gastrointestinal (GI) perforations were reported in 1% of CABOMETYX-treated patients. Monitor patients for symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a fistula which cannot be appropriately managed or a GI perforation.
- **Thrombotic Events:** CABOMETYX treatment results in an increased incidence of thrombotic events. In RCC studies, venous thromboembolism occurred in 9% (including 5% pulmonary embolism) and arterial thromboembolism occurred in 1% of CABOMETYX-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, including hypertensive crisis. In RCC studies, hypertension was reported in 44% (18% Grade ≥ 3) of CABOMETYX-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:** In RCC studies, diarrhea occurred in 74% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 11% of patients treated with CABOMETYX. 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.
- **Palmar-Plantar Erythrodysesthesia (PPE):** In RCC studies, palmar-plantar erythrodysesthesia (PPE) occurred in 42% of patients treated with CABOMETYX. Grade 3 PPE occurred in 8% of patients treated with CABOMETYX. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPE or Grade 3 PPE until improvement to Grade 1; resume CABOMETYX at a reduced dose.
- **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.
- **Embryo-fetal Toxicity** may be associated with CABOMETYX. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during CABOMETYX treatment and for 4 months after the last dose.
- **Adverse Reactions:** The most commonly reported (≥25%) adverse reactions are: diarrhea, fatigue, nausea, decreased appetite, hypertension, PPE, weight decreased, vomiting, dysgeusia, and stomatitis.
- **Strong CYP3A4 Inhibitors**: If concomitant use with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage.
- **Strong CYP3A4 Inducers:** If concomitant use with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage.
- **Lactation:** Advise women not to breastfeed while taking CABOMETYX and for 4 months after the final dose.
- **Hepatic Impairment:** In patients with mild to moderate hepatic impairment, reduce the CABOMETYX dosage. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

Please see accompanying full Prescribing Information 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 these medicines to patients globally. We are steadfast in our commitment to prudently reinvest in our business to maximize the potential of our pipeline. We intend to supplement our existing therapeutic assets 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. Exelixis recently earned a spot on Deloitte's Technology Fast 500 list, a yearly award program honoring the 500 fastest-growing companies over the past four years. For more information about Exelixis, please visit www.exelixis.com, follow @ExelixisInc on Twitter or like Exelixis, Inc. on Facebook.

Exelixis Forward-Looking Statement Disclaimer

This press release contains forward-looking statements, including, without limitation, statements related to: the therapeutic potential of CABOMETYX as a treatment for patients in the European Union diagnosed with previously treated advanced HCC; Exelixis' plan to work with Ipsen to expand the use of CABOMETYX to additional patient populations outside of the current approved indication; Exelixis' expectations regarding the timing of Ipsen's $10 million milestone payment; 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 "potential," "may," "will," "expects," "continue," "commitment," "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: Exelixis' dependence on its relationships with Ipsen, including, the level of Ipsen's 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; Exelixis' dependence on third-party vendors for the development, manufacture and supply of its products; the level of costs associated with Exelixis' commercialization, research and development, in-licensing or acquisition of product candidates, and other activities; competition in the area of business development activities and the inherent uncertainty of the drug discovery process; Exelixis' ability to protect the company's intellectual property rights; market competition, including the potential for competitors to obtain approval for generic versions of Exelixis' marketed products; changes in economic and business conditions, and other factors discussed under the caption "Risk Factors" in Exelixis' annual report on Form 10-K filed with the Securities and Exchange Commission (SEC) on February 26, 2018, 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.

References:

[1] Cancer Incidence and Mortality Worldwide. Liver Cancer. International Agency for Research on Cancer, GLOBOCAN 2012. Available at: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed March 2018.

[2] American Cancer Society: Cancer Facts and Figures 2018. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. Accessed March 2018.

[3] Mittal S, El-Serag HB. Epidemiology of HCC: Consider the Population. *Journal of Clinical Gastroenterology*. 2013. 47:S2-S6.

[4] Weledji E, Orock G, Ngowe M, NsaghaD. How grim is hepatocellular carcinoma? *Annals of Medicine and Surgery*. 2014. 3:71-76.

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