Exelixis' Partner Ipsen Announces Positive CHMP Opinion for CABOMETYX® (cabozantinib) Tablets for Previously Treated Hepatocellular Carcinoma

September 21, 2018

– In the phase 3 pivotal CELESTIAL trial, CABOMETYX demonstrated a statistically significant and clinically meaningful overall survival benefit –

ALAMEDA, Calif.--(BUSINESS WIRE)--Sep. 21, 2018-- Exelixis, Inc. (NASDAQ:EXEL) today announced that its partner Ipsen received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the European Medicines Agency (EMA), for CABOMETYX® (cabozantinib) tablets as a monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have been previously treated with sorafenib. The positive CHMP opinion will now be reviewed by the European Commission, which has the authority to approve medicines for the European Union.

"This positive CHMP opinion represents significant progress for patients in Europe with this aggressive form of liver cancer who progress on prior systemic therapy, a large underserved patient population that currently only has one approved second-line treatment option," said Michael M. Morrissey, Ph.D., President and Chief Executive Officer of Exelixis. "We are excited about the potential therapeutic benefits CABOMETYX may offer the liver cancer community and look forward to the European Commission's decision."

Under the terms of the Collaboration Agreement with Ipsen, Exelixis is eligible to receive a milestone payment of $40 million for the approval of the second-line treatment of HCC. This milestone would be paid by Ipsen within 70 days of the approval decision by the European Commission.

CABOMETYX is currently approved in the European Union for the treatment of advanced renal cell carcinoma (RCC) in adults who have received prior VEGF-targeted therapy and for previously untreated intermediate- or poor-risk advanced RCC. The CHMP recommendation to expand the indication is based on results from the CELESTIAL trial of CABOMETYX in patients with advanced HCC who received prior sorafenib. In this phase 3 pivotal trial, CABOMETYX demonstrated a statistically significant and clinically meaningful improvement in overall survival (OS) versus placebo.

On May 29, 2018, Exelixis announced that the U.S. Food and Drug Administration (FDA) accepted for filing the supplemental New Drug Application (sNDA) for CABOMETYX for previously treated advanced HCC and assigned a Prescription Drug User Fee Act (PDUFA) action date of January 14, 2019. 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 PFS. Exploratory endpoints include patient-reported outcomes, biomarkers and safety.

In October 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, with cabozantinib providing a statistically significant and clinically meaningful improvement in OS compared with placebo in patients with previously treated advanced HCC. The data, originally presented at the 2018 American Society of Clinical Oncology's Gastrointestinal Cancers Symposium (ASCO-GI) in January 2018, were published in *The New England Journal of Medicine* in July 2018.[1]

About HCC

Liver cancer is the second-leading cause of cancer death worldwide, accounting for more than 700,000 deaths and 800,000 new cases each year.[2] In the U.S., the incidence of liver cancer has more than tripled since 1980.[3] 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.[4] HCC is the fastest-rising cause of cancer-related death in U.S.[1] 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 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 VEGF-targeted therapy; in the European Union for previously untreated intermediate- or poor-risk advanced RCC; and in Canada for adult patients

with advanced RCC who have received prior VEGF targeted therapy. In March 2017, the FDA granted orphan drug designation to cabozantinib for the treatment of advanced HCC. On March 28, 2018, Ipsen announced that the European Medicines Agency validated its application for a new indication for cabozantinib as a treatment for previously treated advanced HCC in the European Union; on September 20, 2018 the CHMP provided a positive opinion for CABOMETYX as a monotherapy for the treatment of HCC in adults who have been previously treated with sorafenib. 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.

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 three commercially available products, CABOMETYX® (cabozantinib), COMETRIQ® (cabozantinib) and COTELLIC® (cobimetinib), and have entered into partnerships with leading pharmaceutical companies to bring these important medicines to patients worldwide. Supported by revenues from our marketed products and collaborations, we are committed to prudently reinvesting in our business

to maximize the potential of our pipeline. We are supplementing 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. In July 2018, Exelixis was added to the Standard & Poor's (S&P) MidCap 400 index, which measures the performance of profitable mid-sized companies. For more information about Exelixis, please visit www.exelixis.com, follow @ExelixisInc on Twitter or like Exelixis, Inc. on Facebook.

Forward-Looking Statement Disclaimer

This press release contains forward-looking statements, including, without limitation, statements related to: the regulatory review process in the European Union; the therapeutic potential of CABOMETYX as a treatment option for adult patients in the European Union with advanced HCC who have been previously treated with sorafenib; Exelixis' eligibility to receive a $40 million milestone payment from Ipsen for the approval of CABOMETYX as a treatment for previously treated advanced HCC in the European Union, and the timing for receipt of such payment; 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. Any statements that refer to expectations, projections or other characterizations of future events or circumstances are forward-looking statements and 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, including that the European Commission may not approve cabozantinib as a treatment for previously treated advanced HCC; unexpected concerns that may arise as a result of the occurrence of adverse safety events or additional data analyses of clinical trials evaluating cabozantinib; Exelixis' dependence on its relationships with its collaboration partners, including their pursuit of regulatory approvals for cabozantinib in new indications and their adherence to their obligations under relevant collaboration agreements; Exelixis' ability to protect its intellectual property rights; market competition; changes in economic and business conditions; and other factors affecting the ability of Exelixis and its partners to obtain regulatory approval for cabozantinib in new indications discussed under the caption "Risk Factors" in Exelixis' Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on August 1, 2018, and in Exelixis' future filings with the SEC. All forward-looking statements in this press release are based on information available to Exelixis as of the date of this press release, and Exelixis undertakes no obligation to update or revise any forward-looking statements contained herein.

[1] Abou-Alfa, G, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med.* 2018. 379:54-63.

[2] International Agency for Research on Cancer. GLOBOCAN 2018. Liver Fact Sheet. Available at: http://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf. Accessed September 2018.

[3] 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 September 2018.

[4] Weledji E, Orock G, Ngowe M, NsaghaD. How grim is hepatocellular carcinoma? *Ann Med Surg*. 2014. 3:71-76.

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