Exelixis' Partner Ipsen Announces Health Canada's Approval of CABOMETYX® (cabozantinib) Tablets for the Treatment of Patients With Previously Treated Advanced Hepatocellular Carcinoma

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– Approval based on statistically significant and clinically meaningful overall survival benefit demonstrated in the CELESTIAL phase 3 pivotal trial –

ALAMEDA, Calif.--(BUSINESS WIRE)--Nov. 12, 2019-- Exelixis, Inc. (NASDAQ:EXEL) today announced that its partner Ipsen Biopharmaceuticals Canada Inc. received Health Canada approval of CABOMETYX® (cabozantinib) tablets for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

"Liver cancer is the fourth leading cause of cancer-related death globally, and there is an urgent need for more treatment options for patients living with this aggressive disease," said Michael M. Morrissey, Ph.D., President and Chief Executive Officer of Exelixis. "The Health Canada approval of CABOMETYX brings a much-needed new therapy to Canadian patients with liver cancer and we look forward to our continued collaboration with Ipsen in our efforts to make our medicines available to patients around the world."

The Health Canada approval was based on results from the CELESTIAL phase 3 pivotal trial of CABOMETYX for patients with advanced HCC who received prior treatment with sorafenib. CABOMETYX demonstrated a statistically significant and clinically meaningful improvement in overall survival (OS) versus placebo.

Under the terms of the Collaboration Agreement with Ipsen, Exelixis will receive a milestone payment of $2 million for the Health Canada approval.

CABOMETYX is also approved in Canada for the treatment of adult patients with advanced renal cell carcinoma (RCC) who have received prior vascular endothelial growth factor targeted therapy and for the first-line treatment of adults with intermediate or poor risk advanced RCC.

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 treatment with 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.

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, was published in *The New England Journal of Medicine* in July 2018.[1]

About HCC

Liver cancer is a leading cause of cancer death worldwide, accounting for more than 700,000 deaths and 800,000 new cases each year.[2] The Canadian Cancer Society estimates that 3,000 Canadians will be diagnosed with liver cancer in 2019.[3] In the U.S., the incidence of liver cancer has more than tripled since 1980.[4] 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 2019.[4] HCC is the fastest-rising cause of cancer-related death in the U.S.[5] Without treatment, patients with advanced HCC usually survive less than 6 months.[6]

About the Exelixis and Ipsen Collaboration

In 2016, Exelixis granted Ipsen exclusive rights for the commercialization and further clinical development of cabozantinib outside of the United States and Japan. Under the terms of the Collaboration Agreement with Ipsen, Exelixis is entitled to receive a tiered royalty of 22 percent to 26 percent of annual net sales.

About CABOMETYX® (cabozantinib)

In the U.S., CABOMETYX tablets are approved for the treatment of patients with advanced renal cell carcinoma and for the treatment of patients with HCC who have been previously treated with sorafenib. CABOMETYX tablets have also received regulatory approvals in the European Union and additional countries and regions worldwide. 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 occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.
- **Perforations and Fistulas:** Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of perforations and fistulas, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a fistula that cannot be appropriately managed or a GI perforation.
- **Thrombotic Events:** CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic event requiring medical intervention.
- **Hypertension and Hypertensive Crisis:** CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension occurred in 36% (17% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.
- **Diarrhea:** Diarrhea occurred in 63% of CABOMETYX patients. Grade 3 diarrhea occurred in 11% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 diarrhea, Grade 3 diarrhea that cannot be managed with standard antidiarrheal treatments, or Grade 4 diarrhea.
- **Palmar-Plantar Erythrodysesthesia (PPE):** PPE occurred in 44% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.
- **Proteinuria:** Proteinuria occurred in 7% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. Discontinue CABOMETYX in patients who develop nephrotic syndrome.
- **Osteonecrosis of the Jaw (ONJ):** ONJ occurred in <1% of CABOMETYX patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain, or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 28 days prior to scheduled dental surgery or invasive dental procedures. Withhold CABOMETYX for development of ONJ until complete resolution.
- **Wound Complications:** Wound complications were reported with CABOMETYX. Stop CABOMETYX at least 28 days prior to scheduled surgery. Resume CABOMETYX after surgery based on clinical judgment of adequate wound healing. Withhold CABOMETYX in patients with dehiscence or wound healing complications requiring medical intervention.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, can occur with CABOMETYX. Evaluate for RPLS in patients 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. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX and advise them to use effective contraception during treatment and for 4 months after the last dose.
- **Adverse Reactions:** The most commonly reported (≥25%) adverse reactions are: diarrhea, fatigue, decreased appetite, PPE, nausea, hypertension, and vomiting.
- **Strong CYP3A4 Inhibitors:** If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.
- **Strong CYP3A4 Inducers:** If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John's wort.
- **Lactation:** Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

- **Hepatic Impairment:** In patients with 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 system genetics, 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. Our discovery efforts have resulted in four commercially available products, CABOMETYX® (cabozantinib), COMETRIQ® (cabozantinib), COTELLIC® (cobimetinib) and MINNEBRO® (esaxerenone), and we 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. Exelixis is a member of 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 Statements

This press release contains forward-looking statements, including, without limitation, statements related to: the potential of CABOMETYX as a new therapy for Canadian patients with liver cancer; Exelixis' continued collaboration with Ipsen to make Exelixis medicines available across different indications around the world; the anticipated timing for receipt of a $2 million milestone payment from Ipsen for the Health Canada approval; 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: the degree of market acceptance of CABOMETYX and Ipsen's ability to obtain or maintain coverage and reimbursement for this product; Exelixis' dependence on its relationship with Ipsen, including Ipsen's investment in the resources necessary to successfully commercialize CABOMETYX in the territories where it is approved; Exelixis' and Ipsen's continuing compliance with applicable legal and regulatory requirements; Exelixis' ability to protect its intellectual property rights; Exelixis' dependence on third-party vendors for the manufacture and supply of cabozantinib; market competition, including the potential for competitors to obtain approval for generic versions of CABOMETYX; changes in economic and business conditions; and other factors affecting the ability of Exelixis and its commercial programs and partnerships discussed under the caption "Risk Factors" in Exelixis' Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on October 30, 2019, 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 November 2019.

[3] Canadian Cancer Society: Liver Cancer Statistics. Available at: https://www.cancer.ca/en/cancer-information/cancer-type/liver/statistics/?region=on. Accessed November 2019.

[4] American Cancer Society: Cancer Facts and Figures 2019. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf. Accessed November 2019.

[5] Mittal S, El-Serag HB. Epidemiology of HCC: Consider the Population. *J Clin Gastroenterol*. 2013. 47:S2-S6.

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

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