



Exelixis Announces Partner Takeda Files New Drug Application in Japan for CABOMETRYX® (cabozantinib) for Advanced Hepatocellular Carcinoma

January 29, 2020

– Submission based on two clinical trials in patients with advanced hepatocellular carcinoma who had received prior systemic therapy –

ALAMEDA, Calif.--(BUSINESS WIRE)--Jan. 29, 2020-- [Exelixis, Inc.](#) (NASDAQ: EXEL) today announced that Takeda Pharmaceutical Company Limited (Takeda), its partner responsible for the clinical development and commercialization of CABOMETRYX® (cabozantinib) in Japan, has applied to the Japanese Ministry of Health, Labor and Welfare (MHLW) for Manufacturing and Marketing Approval of cabozantinib as a treatment for patients with unresectable hepatocellular carcinoma (HCC) that had progressed after prior systemic therapy.

Takeda's application is based on the results of two clinical trials in patients with advanced HCC who had received prior systemic therapy: CELESTIAL (XL184-309), a global, randomized, placebo-controlled, double-blind phase 3 clinical trial, and Cabozantinib-2003, a phase 2 clinical trial conducted in Japan.

"We are excited about the progress our partner Takeda has made on advancing cabozantinib toward regulatory approval in Japan for patients with advanced liver cancer," said Michael M. Morrissey, Ph.D., President and Chief Executive Officer of Exelixis. "This regulatory filing is an important milestone for patients in Japan who currently have limited treatment options after they have progressed following systemic therapy. We look forward to our continued collaboration as Takeda works to bring cabozantinib to patients in need of new therapies."

Per the terms of Exelixis and Takeda's collaboration and license agreement, Exelixis is eligible to receive a \$10 million milestone payment from Takeda as a result of this latest submission for HCC, which is anticipated to be received in the first quarter of 2020. In April 2019, Takeda applied for approval to manufacture and sell cabozantinib as a treatment for unresectable and metastatic renal cell carcinoma (RCC) in Japan. Following the milestone associated with this HCC regulatory filing, Exelixis will be eligible to receive further development, regulatory and first-sale milestone payments of up to \$76 million from Takeda related both to previously treated and previously untreated RCC and previously treated HCC. Exelixis continues to be eligible to receive additional development, regulatory and first-sale milestones for potential future cabozantinib indications, and is also eligible for sales revenue milestones and royalties on net sales of cabozantinib in Japan.

Takeda fully funds cabozantinib development activities that are exclusively for the benefit of Japan and is responsible for 20% of the costs associated with global cabozantinib clinical trials, providing the company opts into those trials.

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.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 43,000 new cases in the U.S. in 2020.² HCC is the fastest-rising cause of cancer-related death in the U.S.³ Without treatment, patients with advanced HCC usually survive less than 6 months.⁴

About CABOMETRYX® (cabozantinib)

In the U.S., CABOMETRYX tablets are approved for the treatment of patients with advanced RCC and for the treatment of patients with HCC who have been previously treated with sorafenib. CABOMETRYX tablets have also received regulatory approvals in the European Union and additional countries and regions worldwide. 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.

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

U.S. Important Safety Information

- **Hemorrhage:** Severe and fatal hemorrhages occurred with CABOMETRYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETRYX patients. Discontinue CABOMETRYX for Grade 3 or 4 hemorrhage. Do not administer CABOMETRYX 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 CABOMETRYX patients. Fistulas, including fatal cases, occurred in 1% of CABOMETRYX patients. Monitor patients for signs and symptoms of perforations and fistulas, including abscess and sepsis. Discontinue CABOMETRYX in patients who experience a fistula that cannot be appropriately managed or a GI perforation.
- **Thrombotic Events:** CABOMETRYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETRYX patients. Fatal thrombotic events occurred in CABOMETRYX patients. Discontinue CABOMETRYX 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 ($\geq 25\%$) 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://cabometryx.com/downloads/CABOMETRYXUSPI.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 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.](https://www.facebook.com/ExelixisInc) on Facebook.

Forward-Looking Statements

This press release contains forward-looking statements, including, without limitation, statements related to: the potential for Takeda, as part of its continuing collaboration with Exelixis, to bring CABOMETYX to patients in need of new therapies; the anticipated timing for receipt of a \$10 million milestone payment from Takeda for Takeda's submission of an application to the Japanese MHLW for Manufacturing and Marketing Approval of CABOMETYX as a treatment for patients in Japan with unresectable HCC who progressed after prior systemic therapy; Exelixis' eligibility for future development, regulatory and first-sale milestone payments, plus sales revenue milestones and royalties on net sales under its collaboration with Takeda; 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 Japanese MHLW may not approve CABOMETYX as a treatment for patients with unresectable HCC who progressed after prior systemic therapy; 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; 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' Annual 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.

Exelixis, the Exelixis logo, CABOMETYX, COMETRIQ and COTELLIC are registered U.S. trademarks. MINNEBRO is a Japanese trademark.

¹ 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 January 2020.

² American Cancer Society: Cancer Facts & Figures 2020. Available at: <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf>. Accessed January 2020.

³ Siegel R, Miller K, Jemal A: Cancer Statistics, 2020. CA: A Cancer Journal for Clinicians. Volume 70, Issue 1: 7-30. Available at: <https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21590>. Accessed January 2020.

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

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