Exelixis Announces European Medicines Agency Acceptance of Marketing Authorization Application for Cabozantinib as a Treatment for Advanced Renal Cell Carcinoma

January 28, 2016

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Jan. 28, 2016-- Exelixis, Inc. (NASDAQ:EXEL) today announced the European Medicines Agency (EMA) has accepted for review the Marketing Authorization Application (MAA) for cabozantinib as a treatment for patients with advanced renal cell carcinoma (RCC) who have received one prior therapy. The completion of the MAA validation process confirms that the submission is sufficient to permit a substantive review for marketing authorization in the European Union.

The EMA's Committee for Medicinal Products for Human Use (CHMP) previously granted accelerated assessment to cabozantinib for advanced RCC. As a result, the MAA will be eligible for a 150-day review, versus the standard 210 days (excluding clock stops when information is requested by CHMP).

The MAA is based on the results of METEOR, a phase 3 pivotal trial comparing cabozantinib to everolimus in patients with advanced RCC who experienced disease progression following treatment with a VEGF receptor tyrosine kinase inhibitor. In July 2015, Exelixis announced top-line results from METEOR demonstrating that the trial had met its primary endpoint of improving progression-free survival; compared with everolimus, a standard of care for second line RCC therapy, cabozantinib was associated with a 42% reduction in the rate of disease progression or death. These data were later presented at the European Cancer Congress in September 2015 and concurrently published in *The New England Journal of Medicine*.

In the United States, in late December 2015, Exelixis announced that it completed the submission of its rolling New Drug Application (NDA) for cabozantinib as a treatment for patients with advanced RCC who have received one prior therapy. The U.S. Food and Drug Administration (FDA) subsequently determined the NDA to be sufficiently complete to permit a substantive review, granted Priority Review, and assigned a Prescription Drug User Fee Act action date of June 22, 2016. The NDA will be considered officially filed 60 days from the date of the completion of the submission, or February 20, 2016. The FDA previously granted Breakthrough Therapy and Fast Track designations to cabozantinib for its potential advanced RCC indication.

Cabozantinib is currently marketed in capsule form under the brand name COMETRIQ® in the United States for the treatment of progressive, metastatic medullary thyroid cancer (MTC), and in the European Union for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC. COMETRIQ is not indicated for patients with RCC. In the METEOR trial, and all other cancer trials currently underway, Exelixis is investigating a tablet formulation of cabozantinib distinct from the COMETRIQ capsule form. The tablet formulation of cabozantinib is the subject of the MAA for advanced RCC.

About Advanced Renal Cell Carcinoma

The American Cancer Society's 2015 statistics cite kidney cancer as among the top ten most commonly diagnosed forms of cancer among both men and women in the U.S.[1] Clear cell RCC is the most common type of kidney cancer in adults.[2] If detected in its early stages, the five-year survival rate for RCC is high; however, the five-year survival rate for patients with advanced or late-stage metastatic RCC is under 10 percent, with no identified cure for the disease.[3]

Until the introduction of targeted therapies into the RCC setting a decade ago, treatments for metastatic RCC had historically been limited to cytokine therapy (e.g., interleukin-2 and interferon). In the second and later-line settings, which encompass approximately 17,000 drug-eligible patients in the U.S. and 37,000 globally,[4] two small-molecule therapies and an immune checkpoint inhibitor have been approved for the treatment of patients with advanced RCC who have received prior systemic therapy. The currently approved small-molecule agents have shown little differentiation in terms of efficacy and have demonstrated only modest progression-free survival benefit in patients refractory to sunitinib, a commonly-used first-line therapy.

The majority of clear cell RCC tumors exhibit down-regulation of von Hippel-Lindau protein function, either due to gene inactivation or epigenetic silencing, resulting in a stabilization of the hypoxia-inducible transcription factors and consequent up-regulation of VEGF, MET and AXL.[5] The up-regulation of VEGF may contribute to the angiogenic nature of clear cell RCC, and expression of MET or AXL may be associated with tumor cell viability, a more invasive tumor phenotype and reduced overall survival. [6] Up-regulation of MET and AXL in clear cell RCC has also been shown to occur in response to treatment with VEGF receptor TKIs in preclinical models, indicating a potential role for MET and AXL in the development of resistance to these therapies.[7]

About Cabozantinib

Cabozantinib inhibits the activity of tyrosine kinases including MET, VEGF receptors, AXL and RET. These receptor tyrosine kinases are involved in both normal cellular function and in pathologic processes such as oncogenesis, metastasis, tumor angiogenesis and maintenance of the tumor microenvironment.

Cabozantinib, marketed under the brand name COMETRIQ®, is currently approved by the U.S. Food and Drug Administration for the treatment of progressive, metastatic medullary thyroid cancer (MTC).

The European Commission granted COMETRIQ conditional approval for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC. Similar to another drug approved in this setting, the approved indication states that for patients in whom Rearranged during Transfection (RET) mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decisions.

Important Safety Information, including Boxed WARNINGS

WARNING: PERFORATIONS AND FISTULAS, and HEMORRHAGE

- **Serious and sometimes fatal gastrointestinal perforations and fistulas occur in COMETRIQ-treated patients.**
- **Severe and sometimes fatal hemorrhage occurs in COMETRIQ-treated patients.**
- COMETRIQ treatment results in an increase in thrombotic events, such as heart attacks.
- Wound complications have been reported with COMETRIQ.
- COMETRIQ treatment results in an increase in hypertension.
- Osteonecrosis of the jaw has been observed in COMETRIQ-treated patients.
- Palmar-Plantar Erythrodysesthesia Syndrome (PPES) occurs in patients treated with COMETRIQ.
- The kidneys can be adversely affected by COMETRIQ. Proteinuria and nephrotic syndrome have been reported in patients receiving COMETRIQ.
- Reversible Posterior Leukoencephalopathy Syndrome has been observed with COMETRIQ.
- Avoid administration of COMETRIQ with agents that are strong CYP3A4 inducers or inhibitors.
- COMETRIQ is not recommended for use in patients with moderate or severe hepatic impairment.
- COMETRIQ can cause fetal harm when administered to a pregnant woman.

Adverse Reactions – The most commonly reported adverse drug reactions (≥25%) are diarrhea, stomatitis, palmar-plantar erythrodysesthesia syndrome (PPES), decreased weight, decreased appetite, nausea, fatigue, oral pain, hair color changes, dysgeusia, hypertension, abdominal pain, and constipation. The most common laboratory abnormalities (≥25%) are increased AST, increased ALT, lymphopenia, increased alkaline phosphatase, hypocalcemia, neutropenia, thrombocytopenia, hypophosphatemia, and hyperbilirubinemia.

Please see full U.S. prescribing information, including Boxed WARNINGS, at www.COMETRIQ.com/downloads/Cometriq_Full_Prescribing_Information.pdf.

Please refer to the full European Summary of Product Characteristics for full European Union prescribing information, including contraindication, special warnings and precautions for use at www.sobi.com once posted.

About Exelixis

Exelixis, Inc. is a biopharmaceutical company committed to developing small molecule therapies for the treatment of cancer. Exelixis is focusing its development and commercialization efforts primarily on cabozantinib, its wholly owned inhibitor of multiple receptor tyrosine kinases. Another Exelixis-discovered compound, COTELLIC™ (cobimetinib), a selective inhibitor of MEK, has been approved in Switzerland, the United States, and the European Union, and is being evaluated by Roche and Genentech (a member of the Roche Group) in a broad development program under a collaboration with Exelixis. For more information, please visit the company's website at www.exelixis.com.

Forward-Looking Statement Disclaimer

This press release contains forward-looking statements, including, without limitation, statements related to: the eligibility for an expedited review of the MAA by the EMA; the timing for when the NDA will be considered officially filed; and the potential of cabozantinib as a treatment for patients with advanced RCC. Words such as "will," "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: risks and uncertainties related to regulatory review and approval processes and Exelixis' compliance with applicable legal and regulatory requirements; the clinical, therapeutic and commercial potential of cabozantinib; Exelixis' ability to conduct clinical trials of cabozantinib sufficient to achieve a positive completion; 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 November 10, 2015, and in Exelixis' other 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.

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

[1] *Cancer Facts & Figures 2015. American Cancer Society. Available at http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf*

[2] *Jonasch et al., BMJ (2014) vol. 349, g4797.*

[3] *http://www.cancer.org/cancer/kidneycancer/detailedguide/kidney-cancer-adult-survival-rates*

[4] *ACS Cancer Facts and Figures 2015; Heng et al., Ann Oncol (2012) vol. 23 no. 6; internal data on file; Motzer et al., N Engl J Med (2007) vol. 356 no. 2; NCIN (UK) report, April 2014, Available at http://www.ncin.org.uk/view?rid=2676.*

[5] *Harschman and Choueiri, Cancer J. 2013 v19 316-323; Rankin et al., PNAS, 2014.*

[6] *Bommy-Reddi et al., PNAS, 2008; Gibney et al., Ann. Oncol. 2013 v24 343-349; Koochekpour et al., Mol. Cell. Biol. 1999, v19 5902-5912; Rankin et al., PNAS, 2014.*

[7] *Ciamporcero et al., MolCancerTher, 2014; Rankin et al., PNAS, 2014.*

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