# FDA Grants Breakthrough Therapy Designation to Exelixis' Cabozantinib for the Treatment of Renal Cell Carcinoma in Patients Who Received One Prior Therapy

August 24, 2015

***-- Provides Opportunity to Expedite Regulatory Timelines --***

***-- Exelixis Plans to Complete Submission of Cabozantinib U.S. NDA for Advanced RCC in 2015 --***

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Aug. 24, 2015-- Exelixis, Inc. (NASDAQ:EXEL) today announced the U.S. Food & Drug Administration (FDA) has granted Breakthrough Therapy Designation to cabozantinib, Exelixis' lead compound, as a potential treatment for patients with advanced renal cell carcinoma (RCC) who have received one prior therapy. Created in 2012, FDA's Breakthrough Therapy Designation expedites the development and review of drugs that are intended to treat serious or life-threatening diseases, and for which preliminary clinical evidence indicates the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Drugs that receive Breakthrough Therapy Designation may benefit from involvement of FDA senior managers in the review process, potential rolling submission and/or Priority Review of a sponsor's New Drug Application (NDA), and other benefits.

"Receiving Breakthrough Therapy Designation is an important regulatory achievement for cabozantinib in renal cell carcinoma," said Michael M. Morrissey, Ph.D., president and chief executive officer of Exelixis. "Following the positive top-line results announced in July and a productive dialogue with the FDA, Exelixis believes we can expedite our regulatory timelines and complete the cabozantinib NDA submission in advanced RCC prior to the end of 2015. We look forward to working closely with the FDA during the submission and review process, keeping in mind our ultimate goal of bringing a new therapeutic option to the renal cell carcinoma community as soon as possible."

Cabozantinib received Breakthrough Therapy Designation based on the results of METEOR, the phase 3 pivotal trial comparing cabozantinib to everolimus in patients with RCC who experienced disease progression following treatment with a VEGF receptor tyrosine kinase inhibitor (TKI). In top-line results announced in July 2015, METEOR met its primary endpoint, demonstrating a statistically significant increase in progression-free survival (PFS) for cabozantinib as compared to everolimus in the first 375 patients randomized as determined by an independent radiology review committee. Cabozantinib reduced the rate of disease progression or death by 42 percent compared to everolimus (hazard ratio [HR]=0.58, 95 percent confidence interval [CI] 0.45-0.75, p<0.0001).

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. A distinct tablet formulation of cabozantinib is under investigation for advanced renal cell carcinoma and other types of cancer. COMETRIQ is not indicated for patients with advanced RCC or any other form of the disease.

**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 United States.[1] Clear cell renal cell carcinoma 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]

Treatments for advanced RCC had historically been limited to cytokine therapy (e.g., interleukin-2 and interferon) until the introduction of targeted therapies into the RCC setting a decade ago. In the second and later-line setting, which encompasses approximately 17,000 drug-eligible patients in the U.S. and 37,000 globally,[4] two therapies have been approved for the treatment of patients who have received prior VEGF receptor TKIs. However, despite the availability of several therapeutic options, currently approved agents have shown little differentiation in terms of efficacy and have demonstrated only modest PFS 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 (VHL) protein function, resulting in a stabilization of the hypoxia-inducible transcription factors (HIFs) 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 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 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.

COMETRIQ® (cabozantinib capsules) 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, cobimetinib, a selective inhibitor of MEK, 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 web site at www.exelixis.com.

**Forward-Looking Statements**

This press release contains forward-looking statements that are subject to risk and uncertainty, including, without limitation, that the FDA's grant of Breakthrough Therapy Designation may result in expedited regulatory timelines, Priority Review, and other benefits, which may permit Exelixis to submit an NDA for RCC prior to the end of 2015; that the METEOR trial will continue to the final analysis of OS, which is anticipated in early 2016; and that detailed results of the trial will be presented at an upcoming medical conference. These forward-looking statements are based upon Exelixis' current plans, assumptions, beliefs, expectations, and projections. Actual results and the timing of events could differ materially from those anticipated in the forward-looking statements, which include, without limitation: risks related to the clinical, therapeutic and commercial value of cabozantinib; risks related to Exelixis' ability to conduct clinical trials of cabozantinib sufficient to achieve a positive completion; risks and uncertainties related to regulatory review and approval processes and Exelixis' compliance with applicable legal and regulatory requirements; risks related to 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 August 11, 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.*

[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.*

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