Ipsen and its Partner Exelixis Receive Positive CHMP Opinion for Cabometyx™ (Cabozantinib) for the Treatment of Advanced RCC in Adults Following Prior VEGF-Targeted Therapy

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- **CHMP recommends approval of Cabometyx™ (cabozantinib) for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy based on the results of a large, randomized Phase 3 trial, METEOR**
- **Cabometyx™ (cabozantinib) is the first and only multi-kinase inhibitor with established clinical benefits demonstrated for all three key efficacy endpoints: overall survival (OS), progression-free survival (PFS) and objective response rate (ORR)**
- **Cabometyx™ (cabozantinib) significantly improved overall survival across all evaluated patient subgroups**

PARIS & SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Regulatory News:

Exelixis, Inc. (NASDAQ:EXEL) and Ipsen (Euronext: IPN; ADR: IPSEY) today announced that the Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the European Medicines Agency (EMA) provided a positive opinion for Cabometyx™ (cabozantinib) 20, 40, 60mg for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy and recommended it for marketing authorization. The CHMP positive opinion will now be reviewed by the European Commission (EC), which has the authority to approve medicines for the European Union (EU).

David Meek, Chief Executive Officer of Ipsen, said: *"We are pleased that European patients with renal cell cancer may soon have access to Cabometyx™ Ipsen is very proud to receive this positive CHMP opinion for Cabometyx™, a new drug with unprecedented clinical results in the treatment of advanced renal cell carcinoma. Cabometyx™ has demonstrated robust and consistent benefits regardless of prior treatment, location and extent of tumor metastases in previously treated patients suffering from advanced renal cell carcinoma."*

"The positive CHMP opinion for Cabometyx™ is a significant milestone for both Exelixis and Ipsen as we work together to bring this important treatment option to patients with advanced renal cell carcinoma," said **Michael M. Morrissey, Ph.D., President and Chief Executive Officer of Exelixis.** *"With our shared mission of delivering innovative therapies to improve the treatment of cancer, we have the opportunity to change the way this patient population is treated. If approved by the European Commission, Cabometyx™ will provide a new treatment option with proven clinically significant benefit across all three efficacy endpoints addressing a serious unmet medical need."*

The positive CHMP opinion was adopted following an accelerated review procedure reserved for medicinal products expected to be of major public health interest. The recommendation will now be reviewed by the European Commission, which has the authority to approve medicines for use in the 28 countries of the European Union, Norway and Iceland, with a decision expected two months post CHMP opinion.

The detailed recommendations for the use of this product will be described in the Summary of Product Characteristics (SmPC), to be made available if the medication receives marketing authorization from the European Commission.

On January 28, 2016, the European Medicines Agency (EMA) validated Exelixis' Marketing Authorization Application (MAA) for Cabometyx™ (cabozantinib) as a treatment for patients with advanced renal cell carcinoma who have received one prior therapy. The MAA has been granted accelerated assessment, making it eligible for a 150-day review, versus the standard 210 days. On February 29, 2016, Exelixis and Ipsen jointly announced an exclusive licensing agreement for the commercialization and further development of cabozantinib indications outside of the United States, Canada and Japan.

On April 25, 2016 Cabometyx™ (cabozantinib) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with advanced RCC who have received prior anti-angiogenic therapy.

About the METEOR Phase 3 Pivotal Trial
METEOR was an open-label, event-driven trial of 658 patients with advanced renal cell carcinoma who had failed at least one prior VEGFR TKI therapy. The primary endpoint was PFS in the first 375 patients treated. Secondary endpoints included OS and objective response rate in all enrolled patients. The trial was conducted at approximately 200 sites in 26 countries, and enrollment was weighted toward Western Europe, North America, and Australia. Patients were randomized 1:1 to receive 60 mg of Cabometyx™ (cabozantinib) daily or 10 mg of everolimus daily and were stratified based on the number of prior VEGFR TKI therapies received and on MSKCC risk criteria. No cross-over was allowed between the study arms.

METEOR met its primary endpoint of significantly improving PFS. Compared with everolimus, Cabometyx™ (cabozantinib) was associated with a 42 percent reduction in the rate of disease progression or death. Median PFS for Cabometyx™ (cabozantinib) was 7.4 months versus 3.8 months for everolimus (HR=0.58, 95% CI 0.45-0.74, P<0.0001). Cabometyx™ (cabozantinib) also significantly improved the objective response rate compared with everolimus (p<0.0001). These data were presented at the European Cancer Congress in September 2015 and published in *The New England Journal of Medicine*.1

Cabometyx™ (cabozantinib) also demonstrated a statistically significant and clinically meaningful increase in OS in the METEOR trial. Compared with everolimus, Cabometyx™ (cabozantinib) was associated with a 34 percent reduction in the rate of death. Median OS was 21.4 months for patients receiving Cabometyx™ (cabozantinib) versus 16.5 months for those receiving everolimus (HR=0.66, 95% CI 0.53-0.83, P=0.0003).

Cabometyx™ (cabozantinib) benefit in OS was robust and consistent across all pre-specified subgroups. In particular, benefit was observed

regardless of risk category, location and extent of tumor metastases, and tumor MET expression level. These results were presented on June 5, 2016 at the ASCO Annual Meeting and concurrently published in *The Lancet Oncology*.2

At the time of the analysis, the median duration of treatment in the trial was 8.3 months with Cabometyx™ (cabozantinib) versus 4.4 months with everolimus. The most frequent adverse events regardless of causality were diarrhea, fatigue, decreased appetite and hypertension for Cabometyx™ and fatigue, anemia, decreased appetite and cough for everolimus. Dose reductions occurred for 62 percent and 25 percent of patients, respectively. Discontinuation rate due to an adverse event not related to disease progression was 12 percent with Cabometyx™ (cabozantinib) and 11 percent with everolimus.

About Advanced Renal Cell Carcinoma
Renal cell carcinoma (RCC) represents 2-3% of all cancers3, with the highest incidence occurring in Western countries. Generally, during the last two decades until recently, there has been an annual increase of about 2% in incidence both worldwide and in Europe, though in Denmark and Sweden a continuing decrease has been observed4. In 2012, there were approximately 84,400 new cases of RCC and 34,700 kidney cancer related deaths within the European Union5. In Europe, overall mortality rates for RCC have increased up until the early 1990s, with rates generally stabilizing or declining thereafter6. There has been a decrease in mortality since the 1980s in Scandinavian countries and since the early 1990s in France, Germany, Austria, the Netherlands, and Italy. However, in some European countries (Croatia, Estonia, Greece, Ireland, Slovakia), mortality rates still show an upward trend with increasing rates6.

The majority of clear cell RCC tumors have lower than normal levels of a protein called von Hippel-Lindau, which leads to higher levels of MET, AXL and VEGF.7,8 These proteins promote tumor angiogenesis (blood vessel growth), growth, invasiveness and metastasis.9-12 MET and AXL may provide escape pathways that drive resistance to VEGFR inhibitors.8,9

About CABOMETYX™ (cabozantinib)
Cabometyx™ (cabozantinib) targets include MET, AXL and VEGFR-1, -2 and -3. In preclinical models, cabozantinib has been shown to inhibit the activity of these receptors, which are involved in normal cellular function and pathologic processes such as tumor angiogenesis, invasiveness, metastasis and drug resistance.

About Exelixis
Exelixis, Inc. (NASDAQ: EXEL) is a biopharmaceutical company committed to the discovery, development and commercialization of new medicines with the potential to improve care and outcomes for people with cancer. Since its founding in 1994, three medicines discovered at Exelixis have progressed through clinical development to receive regulatory approval. Currently, Exelixis is focused on advancing cabozantinib, an inhibitor of multiple tyrosine kinases including MET, AXL and VEGF receptors, which has shown clinical anti-tumor activity in more than 20 forms of cancer and is the subject of a broad clinical development program. Two separate formulations of cabozantinib have received regulatory approval to treat certain forms of kidney and thyroid cancer and are marketed for those purposes as CABOMETYX™ tablets (U.S.) and COMETRIQ® capsules (U.S. and EU), respectively. Another Exelixis-discovered compound, COTELLIC™ (cobimetinib), a selective inhibitor of MEK, has been approved in major territories including the United States and European Union, and is being evaluated for further potential indications by Roche and Genentech (a member of the Roche Group) under a collaboration with Exelixis. For more information on Exelixis, please visit www.exelixis.com or follow @ExelixisInc on Twitter.

About Ipsen
Ipsen is a global specialty-driven pharmaceutical group with total sales exceeding €1.4 billion in 2015. Ipsen sells more than 20 drugs in more than 115 countries, with a direct commercial presence in more than 30 countries. Ipsen's ambition is to become a leader in specialty healthcare solutions for targeted debilitating diseases. Its fields of expertise cover oncology, neurosciences and endocrinology (adult & pediatric). Ipsen's commitment to oncology is exemplified through its growing portfolio of key therapies improving the care of patients suffering from prostate cancer, bladder cancer and neuro-endocrine tumors. Ipsen also has a significant presence in primary care. Moreover, the Group has an active policy of partnerships. Ipsen's R&D is focused on its innovative and differentiated technological platforms, peptides and toxins, located in the heart of the leading biotechnological and life sciences hubs (Les Ulis/Paris-Saclay, France; Slough/Oxford, UK; Cambridge, US). In 2015, R&D expenditures neared €193 million. The Group has more than 4,600 employees worldwide. Ipsen's shares are traded on segment A of Euronext Paris (stock code: IPN, ISIN code: FR0010259150) and are eligible to the "Service de Règlement Différé" ("SRD"). The Group is part of the SBF 120 index. Ipsen has implemented a Sponsored Level I American Depositary Receipt (ADR) program, which trades on the over-the-counter market in the United States under the symbol IPSEY. For more information on Ipsen, visit www.ipsen.com.

Exelixis Forward-Looking Statement Disclaimer
This press release contains forward-looking statements, including, without limitation, statements related to: the review by the EC of the CHMP's positive opinion for CabometyxTM (cabozantinib) 20, 40, 60mg for te treatment of advanced RCC in adults following prior VEGF-targeted therapy; the potential for European patients with RCC to soon have access to CabometyxTM; Exelixis' shared mission with Ipsen to deliver innovative therapies to improve the treatment of cancer; the opportunity to change the way the RCC patient population is treated the potential for Cabometyx™ to provide a new treatment option with proven clinically significant benefit across all three efficacy endpoints addressing a serious unmet medical need, if approved by the EC; the expectation that the EC will issue a decision on the approval of CabometyxTM in two months; Exelixis' plan to work with the European Commission to complete the review process for COMETRIQ's proposed indication as a treatment for progressive, unresectable locally advanced or metastatic MTC; the potential approval by the European Commission of the proposed indication of COMETRIQ for the treatment of progressive, unresectable locally advanced or metastatic MTC;; Exelixis' commitment to the discovery, development and commercialization of new medicines with the potential to improve care and outcomes for people with cancer; Exelixis' focus on advancing cabozantinib; and the continued development of cobimetinib. Words such as "will," "may," "mission," "opportunity," "expected," "committed," "potential," "focused," 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; Exelixis' dependence on its relationship with Ipsen, including, the level of Ipsen's investment in the resources necessary to successfully commercialize cabozantinib in the territories where it is approved; the risk that unanticipated developments could adversely affect the commercialization of CABOMETYX; Exelixis' ability to conduct clinical trials of cabozantinib sufficient to achieve a positive completion; risks related to the potential failure of cabozantinib to demonstrate safety and efficacy in clinical testing; Exelixis' dependence on its relationship with Genentech/Roche with respect to cobimetinib and Exelixis' ability to maintain its rights

under the collaboration; 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' annual report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on May 4, 2016, and in Exelixis' future 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.

Ipsen Forward Looking Statement
The forward-looking statements, objectives and targets contained herein are based on the Group's management strategy, current views and assumptions. Such statements involve known and unknown risks and uncertainties that may cause actual results, performance or events to differ materially from those anticipated herein. All of the above risks could affect the Group's future ability to achieve its financial targets, which were set assuming reasonable macroeconomic conditions based on the information available today. Use of the words "believes," "anticipates" and "expects" and similar expressions are intended to identify forward-looking statements, including the Group's expectations regarding future events, including regulatory filings and determinations. Moreover, the targets described in this document were prepared without taking into account external growth assumptions and potential future acquisitions, which may alter these parameters. These objectives are based on data and assumptions regarded as reasonable by the Group. These targets depend on conditions or facts likely to happen in the future, and not exclusively on historical data. Actual results may depart significantly from these targets given the occurrence of certain risks and uncertainties, notably the fact that a promising product in early development phase or clinical trial may end up never being launched on the market or reaching its commercial targets, notably for regulatory or competition reasons. The Group must face or might face competition from generic products that might translate into a loss of market share. Furthermore, the Research and Development process involves several stages each of which involves the substantial risk that the Group may fail to achieve its objectives and be forced to abandon its efforts with regards to a product in which it has invested significant sums. Therefore, the Group cannot be certain that favourable results obtained during pre-clinical trials will be confirmed subsequently during clinical trials, or that the results of clinical trials will be sufficient to demonstrate the safe and effective nature of the product concerned. There can be no guarantees a product will receive the necessary regulatory approvals or that the product will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements. Other risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the Group's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the Group's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions. The Group also depends on third parties to develop and market some of its products which could potentially generate substantial royalties; these partners could behave in such ways which could cause damage to the Group's activities and financial results. The Group cannot be certain that its partners will fulfil their obligations. It might be unable to obtain any benefit from those agreements. A default by any of the Group's partners could generate lower revenues than expected. Such situations could have a negative impact on the Group's business, financial position or performance. The Group expressly disclaims any obligation or undertaking to update or revise any forward looking statements, targets or estimates contained in this press release to reflect any change in events, conditions, assumptions or circumstances on which any such statements are based, unless so required by applicable law. The Group's business is subject to the risk factors outlined in its registration documents filed with the French Autorité des Marchés Financiers.

The risks and uncertainties set out are not exhaustive and the reader is advised to refer to the Group's 2015 Registration Document available on its website (www.ipsen.com).

References

1. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015; 373(19):1814-1823.
2. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Onc. 2016 Jun 5; S1470-2045(16)30107-3.
3. European Network of Cancer Registries. Eurocim version 4.0. European incidence database V2.3, 730 entity dictionary (2001), Lyon, 2001.
4. Lindblad P. Epidemiology of renal cell carcinoma. Scand J Surg 2004;93(2):88-96 http://www.ncbi.nlm.nih.gov/pubmed/15285559
5. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013 Apr;49(6):1374-403. http://www.ncbi.nlm.nih.gov/pubmed/23485231
6. Levi F, Ferlay J, Galeone C, et al. The changing pattern of kidney cancer incidence and mortality in Europe. BJU Int 2008 Apr;101(8):949-58 http://www.ncbi.nlm.nih.gov/pubmed/18241251
7. Harshman, L.C. and Choueiri, T.K., Targeting the hepatocyte growth factor/c-Met signaling pathway in renal cell carcinoma. Cancer J. 2013; 19(4):316-323.
8. Rankin et al., Direct regulation of GAS6/AXL signaling by HIF promotes renal metastasis through SRC and MET. Proc Natl Acad Sci U S A. 2014; 111(37):13373-13378.
9. Zhou L, Liu X-D, Sun M, et al. Targeting MET and AXL overcomes resistance to sunitinib therapy in renal cell carcinoma. Oncogene. 2015 Sep 14. doi:10.1038/onc.2015.343. [Epub ahead of print].
10. Koochekpour et al.,The von Hippel-Lindau tumor suppressor gene inhibits hepatocyte growth factor/scatter factor-induced invasion and branching morphogenesis in renal carcinoma cells. Mol Cell Biol. 1999; 19(9):5902–5912.
11. Takahashi A, Sasaki H, Kim SJ, et al. Markedly increased amounts of messenger RNAs for vascular endothelial growth factor and placenta growth factor in renal cell carcinoma associated with angiogenesis. Cancer Res. 1994;54:4233-4237.
12. Nakagawa M, Emoto A, Hanada T, Nasu N, Nomura Y. Tubulogenesis by microvascular endothelial cells is mediated by vascular endothelial growth factor (VEGF) in renal cell carcinoma. Br J Urol. 1997;79:681-687.

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