European Commission approves Ipsen's Cabometyx™ (cabozantinib) Tablets for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy

- **Cabometyx™ (cabozantinib) is the first and only targeted therapy to improve Overall Survival (OS), Objective Response Rate (ORR), and Progression Free Survival (PFS) in RCC in METEOR randomized Phase 3 trial**

- **Cabometyx™ (cabozantinib) improves OS across all evaluated patient subgroups**

- **Cabometyx™ (cabozantinib) has a unique mechanism of action with the potential to overcome resistance to VEGFR tyrosine kinase inhibitors**

Paris, France, 14 September 2016 – Ipsen (Euronext: IPN; ADR: IPSEY), a global specialty-driven pharmaceutical group, today announced that the European Commission has approved Cabometyx™ (cabozantinib) 20, 40, 60 mg tablets for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy. Cabometyx™ (cabozantinib) is the only single agent to demonstrate significant clinical benefits across all three efficacy endpoints (OS, PFS, ORR) in a phase 3 study in previously treated patients with RCC. This approval allows for the marketing of Cabometyx™ (cabozantinib) in previously treated advanced RCC in all 28 member states of the European Union, Norway and Iceland.

David Meek, Chief Executive Officer, Ipsen stated: *"The approval of Cabometyx™ (cabozantinib) in Europe provides a breakthrough treatment to physicians and their patients suffering from renal cancer who failed on initial therapy. This oral drug has the potential to become a new standard of care in the second line setting of advanced renal cell carcinoma as it prolongs survival, slows disease progression, and shrinks tumors, with a clinically-acceptable safety and tolerability profile."*

Dr. Bernard Escudier, oncologist, kidney cancer and immunotherapy specialist at Institut Gustave Roussy, Villejuif (France) added: *"The approval of Cabometyx™ (cabozantinib) by the European Commission brings a new treatment option offering survival benefit for patients with renal cancer who failed a prior treatment with a VEGFR-targeted therapy. This oral drug, in addition to targeting VEGF, has a unique mechanism of action targeting MET and AXL which are common pathways of resistance in renal cell carcinoma. Cabometyx™ also offers a convenient oral schedule for patients and flexibility of dosing for individualized treatment. "*

The approval is based on the results of a large, randomized phase 3 trial METEOR.

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 tyrosine kinase activity of these receptors, which are involved in normal cellular function and pathologic processes such as tumor angiogenesis, invasiveness, metastasis and drug resistance.

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

On September 9, 2016, the European Commission approved Cabometyx™ (cabozantinib) for the treatment of advanced renal cell carcinoma in adults who have received prior vascular endothelial growth factor (VEGF)-targeted therapy in the European Union, Norway and Iceland.

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.

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 randomized. 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 by 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, be it through investigator assessment (24% versus 4%, p<0.0001) or through central review (17% versus 3%, 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 cancers[3], 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 observed[4]. In 2012, there were approximately 84,400 new cases of RCC and 34,700 kidney cancer related deaths within the European Union[5]. In Europe, overall mortality rates for RCC have increased up until the early 1990s, with rates generally stabilizing or declining thereafter[6]. 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 rates[6].

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 Ipsen in oncology

Ipsen focuses its efforts in fighting cancers such as prostate cancer or those with high unmet medical needs such as bladder cancer, neuroendocrine tumors, kidney cancer and other niche oncology diseases. Our ambition is to offer new therapeutic options to patients and caregivers in

their treatment journeys. Ipsen has a continuous commitment in innovative treatment development in oncology through an open innovation approach and using differentiated technological platforms notably in peptides. Moreover Ipsen has built scientific partnerships with trusted academic institutions, leading pharmaceutical and biotech companies and work with today's top researchers and clinicians. We thus develop effective and innovative therapeutic solutions to improve treatment outcomes for patients and to support healthcare professionals in their daily practice.

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 expenditure totaled close to €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 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 trade on the over-the-counter market in the United States under the symbol IPSEY. For more information on Ipsen, visit www.ipsen.com.

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).

For further information:

Ipsen
Media

Didier Véron
Senior Vice-President, Public Affairs
and Communication
Tel.: +33 (0)1 58 33 51 16
E-mail: didier.veron@ipsen.com

Brigitte Le Guennec
Corporate External Communication Manager
Tel.: +33 (0)1 58 33 51 17
E-mail : brigitte.le.guennec@ipsen.com

Financial Community

Eugenia Litz
Vice-President Investor Relations
Tel.: +44 (0) 1753 627721
E-mail: eugenia.litz@ipsen.com

Côme de La Tour du Pin
Investor Relations Executive
Tel.: +33 (0)1 58 33 53 31
E-mail: come.de.la.tour.du.pin@ipsen.com

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