Press Release

Ipsen receives positive CHMP opinion for Cabometyx® in previously treated advanced neuroendocrine tumors

- If approved, Cabometyx® would be the first and only systemic therapy approved in the European Union for previously treated neuroendocrine tumors, regardless of tumor site, grade or previous non-somatostatin analogue-based systemic therapy[1,2]
- Recommendation based on CABINET Phase III trial results, which demonstrated statistically significant and clinically meaningful reductions in risk of disease progression or death with Cabometyx versus placebo[3,4]
- European Commission decision expected Q3 2025

PARIS, FRANCE, 20 June 2025 - Ipsen (Euronext: IPN; ADR: IPSEY) announced today that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has issued a positive opinion for Cabometyx® (cabozantinib) for adult patients with unresectable or metastatic, well differentiated extra-pancreatic (epNET) and pancreatic (pNET) neuroendocrine tumors who have progressed following at least one prior systemic therapy other than somatostatin analogues. This recommendation is based on results from the CABINET Phase III trial presented at the European Society of Medical Oncology (ESMO) Congress 2024 and published in the *New England Journal of Medicine*.[3,4] A final decision on the approval in the European Union is expected in the coming months.

The number of people newly diagnosed with neuroendocrine tumors (NETs) is believed to be increasing, with a higher estimated prevalence than pancreatic or bladder cancer.[5,6,7] Most forms of NETs develop slowly and can originate in various parts of the body,[8] often requiring multiple lines of therapy as the disease progresses.[1,2] Treatment options upon progression are often limited depending on primary tumor site and other factors, making it challenging to define optimal sequencing of treatments specific to individual patient needs.[1,2,9] In particular, for the 27% of people diagnosed with lung NETs,[10] there are no approved treatment options available upon progression on a non-somatostatin analogue-based systemic therapy.[1,2]

“The significant efficacy data demonstrated in the CABINET Phase III trial have provided the opportunity to reframe conversations on care approaches for people living with advanced pancreatic and extra-pancreatic neuroendocrine tumors,” said Christelle Huguet, PhD, EVP and Head of Research and Development, Ipsen. “Today's positive CHMP opinion confirms the potential to translate these data into meaningful benefits for patients and we look forward to receiving the final decision from the European Commission.”

The five-year survival rate is highly dependent on the primary site of disease. For advanced gastrointestinal and lung NETs, where the cancer has spread to distant parts of the body, the five-year survival rates are 68% and 55%, respectively.[11,12] For people diagnosed with advanced pNET, however, the prognosis is poor, with a five-year survival rate of 23%.[13]

The positive CHMP opinion is based on data from the CABINET Phase III trial, which investigated Cabometyx versus placebo in people living with advanced pNETs or epNETs, whose disease had progressed after prior systemic therapy other than somatostatin analogues.[3,4]

- In the pNET cohort, at a median follow-up of 13.8 months, median PFS was 13.8 months for Cabometyx versus 4.4 months for placebo (hazard ratio (HR) 0.23 [95% confidence interval (CI) 0.12-0.42] p<0.001).[3,4]

- In the epNET cohort, at a median follow-up of 10.2 months, median PFS based on local radiology review was 8.4 months for Cabometyx versus 3.9 months for placebo (HR 0.38 [95% CI 0.25-0.59] p<0.001).[3,4]
- Overall survival data were not mature at the time of the analyses and potentially confounded by the crossover design of the CABINET trial.[3,4]
- The safety profile of Cabometyx observed in each cohort was consistent with its known safety profile; no new safety signals were identified.[3,4]
- Per presentation at the Annual Society of Clinical Oncology Annual Meeting 2025, health-related quality of life was also found to be maintained or improved.[14]

About Cabometyx

Cabometyx is a small molecule that inhibits multiple receptor tyrosine kinases, including VEGFRs, MET, RET and the TAM family (TYRO3, MER, AXL).[15] These receptor tyrosine kinases are involved in both normal cellular function and pathological processes such as oncogenesis, metastasis, tumor angiogenesis (the growth of new blood vessels that tumors need to grow), drug resistance, immune modulation, and maintenance of the tumor microenvironment.[15,16,17,18]

Exelixis granted Ipsen exclusive rights for the commercialization and further clinical development of Cabometyx outside of the U.S. and Japan. Exelixis granted exclusive rights to Takeda Pharmaceutical Company Limited (Takeda) for the commercialization and further clinical development of Cabometyx for all future indications in Japan. Exelixis holds the exclusive rights to develop and commercialize Cabometyx in the U.S.

In over 65 countries outside of the United States and Japan, including in the European Union, Cabometyx is currently indicated as:[16]

- Monotherapy for advanced renal cell carcinoma (aRCC).
    - as first-line treatment of adults with intermediate- or poor-risk disease.
    - in adults following prior VEGFR-targeted therapy.
- A combination with nivolumab for the first-line treatment of aRCC in adults.
- Monotherapy for the treatment of adults living with locally advanced or metastatic differentiated thyroid carcinoma, refractory or not eligible to radioactive iodine who have progressed during or after prior systemic therapy.
- Monotherapy for the treatment of hepatocellular carcinoma in adults who have previously been treated with sorafenib.

About CABINET (Alliance A021602)

CABINET (randomized, double-blinded Phase III trial of CABozantinib versus placebo In patients with advanced NEuroendocrine Tumors after progression on prior therapy) is sponsored by the National Cancer Institute (NCI), part of the National Institutes of Health in the U.S., and is being led and conducted by the NCI-funded Alliance for Clinical Trials in Oncology with participation from the NCI-funded National Clinical Trials Network, as part of Exelixis' collaboration through a Cooperative Research and Development Agreement with the NCI's Cancer Therapy Evaluation Program.

The multicenter, Phase III CABINET pivotal trial enrolled a total of 298 patients in the U.S. at the time of the analysis. Patients were randomized 2:1 to Cabometyx or placebo in two separately powered cohorts. The epNET cohort included patients with the following primary tumor sites: gastrointestinal tract, lung, unknown primary and other organs. Each cohort was randomized separately and had its own statistical analysis plan. Patients must have had measurable disease per RECIST 1.1 criteria and must have experienced disease progression or intolerance after at least one U.S. Food and Drug Administration-approved line of prior systemic therapy other than somatostatin analogues. The primary endpoint in each cohort was PFS per RECIST 1.1 by retrospective independent central review.

Upon confirmation of disease progression, patients were unblinded, and those receiving placebo were permitted to cross over to open-label therapy with Cabometyx. Secondary endpoints included overall survival, objective response rate and safety. More information about this trial is available at ClinicalTrials.gov.

About Ipsen

We are a global biopharmaceutical company with a focus on bringing transformative medicines to patients in three therapeutic areas: Oncology, Rare Disease and Neuroscience.

Our pipeline is fueled by external innovation and supported by nearly 100 years of development experience and global hubs in the U.S., France and the U.K. Our teams in more than 40 countries and our partnerships around the world enable us to bring medicines to patients in more than 100 countries.

Ipsen is listed in Paris (Euronext: IPN) and in the U.S. through a Sponsored Level I American Depositary Receipt program (ADR: IPSEY). For more information, visit ipsen.com.

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Ipsen's patents and other protections for innovative medicines; and the exposure to litigation, including patent litigation, and/or regulatory actions. Ipsen also depends on third parties to develop and market some of its medicines which could potentially generate substantial royalties; these partners could behave in such ways which could cause damage to Ipsen's activities and financial results. Ipsen 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 Ipsen's partners could generate lower revenues than expected. Such situations could have a negative impact on Ipsen's business, financial position or performance. Ipsen expressly disclaims any obligation or undertaking to update or revise any forwardlooking 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. Ipsen'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 Ipsen's latest Universal Registration Document, available on ipsen.com.

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