

Ipsen's Somatuline[®] Depot[®] is the first therapy approved by the FDA in the United States for the treatment of patients with locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors

- **FDA approved Somatuline[®] Depot[®] 120mg (lanreotide) Injection for the treatment of pancreatic and gastrointestinal neuroendocrine tumors to improve progression free survival**
- **US organization ready for launch in Q1 2015**

Paris (France), 16 December 2014 – Ipsen (Euronext: IPN; ADR: IPSEY) today announced that Somatuline[®] Depot[®] (lanreotide) Injection 120 mg (referred to as Somatuline[®]) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of adult patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

Marc de Garidel, Chairman and Chief Executive Officer of Ipsen stated: *"I am pleased with the approval by the FDA of this new indication for Somatuline[®], which is a testimony to the scientific quality of those clinical results. Ipsen is now prepared to launch in the US the first antitumor therapeutic approved for the treatment of both pancreatic and gastrointestinal neuroendocrine tumors. This represents a significant step forward in the treatment of this cancer, which affects thousands of Americans. In the US, we have diligently built a robust commercial organization that will execute on the launch of Somatuline[®] in this indication in early 2015."* **Marc de Garidel** concluded: *"Today marks a major strategic milestone in our history, as we are now in a position to fully leverage our presence in the US."*

Pr Martyn Caplin, Professor of Gastroenterology & Gastrointestinal Neuroendocrinology, Royal Free Hospital (London, UK) and Principal Investigator of CLARINET[®], commented: *"Somatuline[®] has shown substantial clinical benefit in treating both pancreatic and gastrointestinal neuroendocrine tumors and can be considered as a first line therapy in the treatment of those tumors. This rapid approval from the FDA is welcome news for NET patients, their families and the whole NET community. I am looking forward to further regulatory approvals around the world so that patients with pancreatic and gastrointestinal neuroendocrine tumors can have access to this effective and well tolerated therapy."*



Somatuline[®] was previously approved in the United States for the long-term treatment of acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option.

Somatuline[®]'s approval was based on demonstration of improved progression-free survival (PFS) in CLARINET[®] multi-center, international, randomized (1:1), double-blind, placebo-controlled study that enrolled 204 patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic, non-functioning GEP-NETs. Patients were randomized to receive either Somatuline[®] (lanreotide) 120 mg or placebo subcutaneously every 28 days. The primary efficacy endpoint was PFS as determined by independent central radiology review. The trial demonstrated a significant prolongation of PFS for the Somatuline[®] (lanreotide) arm [HR 0.47 (95% CI: 0.30, 0.73); $p < 0.001$; stratified log-rank test]. The median PFS in the Somatuline[®] (lanreotide) arm had not been reached at the time of the final analysis and therefore is greater than 22 months. The median PFS in the placebo arm was 16.6 months. Safety data were evaluated in 101 patients who received at least one dose of Somatuline[®] (lanreotide). The most commonly (greater than or equal to 10%) reported adverse reactions in Somatuline[®] (lanreotide)-treated patients were abdominal pain, musculoskeletal pain, vomiting, headache, injection site reaction, hyperglycemia, hypertension, and cholelithiasis. The most common serious adverse reaction of Somatuline[®] (lanreotide) observed in this trial was vomiting (4%).

The recommended dose and schedule for Somatuline[®] (lanreotide) for GEP-NET is lanreotide 120 mg administered by deep subcutaneous injection every 28 days. Treatment should continue until disease progression or unacceptable toxicity.

About Pancreatic and Gastrointestinal Neuroendocrine Tumors

Pancreatic and gastrointestinal neuroendocrine tumors are rare cancers. There are an estimated 112,000 individuals^{1,2} currently living with pancreatic and gastrointestinal neuroendocrine tumors in the U.S., and the incidence and prevalence of this type of cancer have risen 4-to-6 fold in the last 30 years³. Furthermore, up to ninety percent of patients are diagnosed at a late stage.⁴

About CLARINET[®]

CLARINET[®] was an Phase III, randomized, double-blind, placebo-controlled study of lanreotide's antiproliferative response in patients with enteropancreatic neuroendocrine tumors (ClinicalTrials.gov NCT00353496). This 96-week multinational study was conducted in collaboration with the UK & Ireland Neuroendocrine Tumour Society (UKI NETS) and the European Neuroendocrine Tumour Society

¹ Öberg, K, Knigge, U, Kwekkeboom, D, Perren, A, (2012). Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, 23(Supplement 7), 124-130

² United States Census Bureau. Census Website. <http://www.census.gov/popclock/>. Accessed December 10, 2014.

³ Lawrence B, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM (2011). The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinology and Metabolism Clinics of North America*, 40(1), 1-18, vii

Yao JC, Hassan M, Phan AT, et al. (2008) One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *Journal of Clinical Oncology*; 26(18), 3063-3072

⁴ Center for Carcinoid and Neuroendocrine Tumors. Mount Sinai Hospital Website: <http://www.mountsinai.org/patient-care/service-areas/digestive-disease/areas-of-care/neuroendocrine-tumors>. Accessed October 14, 2014



(ENETS). CLARINET[®] results were published in the July 17th, 2014 issue of The New England Journal of Medicine⁵.

A total of 204 patients from 48 centers across 14 countries with well or moderately differentiated non-functioning enteropancreatic neuroendocrine tumors and a proliferation index (Ki67) of <10%, were randomized to treatment with Somatuline[®] 120 mg every 4 weeks (n=101) or placebo (n=103). At enrollment, primary tumor locations were pancreas (45%), midgut (36%), hindgut (7%) and unknown (13%). Thirty percent of patients had a Ki67 of 3% to 10% (WHO grade 2) and 33% had a hepatic tumor load >25%.

The primary efficacy endpoint was time to either disease progression (centrally assessed using Response Evaluation Criteria In Solid Tumors, RECIST 1.0) or death. Two baseline computed tomography scans were performed, followed by additional scans (tomography or magnetic resonance imaging) at 12-week intervals during the first year and 24-week intervals during the second year of study up to week 96.

The data showed that placebo-treated patients had a median PFS of 16.6 months and 33.0% had not progressed or died at 96 weeks, whereas the median PFS for Somatuline[®] treated patients was not reached and 65.1% had not progressed or died at 96 weeks (stratified logrank test, p<0.001). This represented a 53% reduction in risk of disease progression or death based on a hazard ratio of 0.47 (95% CI: 0.30-0.73). These statistically and clinically significant antitumoral effects of Somatuline[®] were observed in a large population of patients with grade G1 or G2 (Ki-67 < 10%; World Health Organization 2010 classification) GEP-NETs. Overall survival and quality of life measures were not different between the Somatuline[®] and placebo groups. Safety data generated from the study are consistent with the known safety profile of Somatuline[®]. Most common adverse reactions (>10%) are abdominal pain (34%), musculoskeletal pain (19%), vomiting (19%), headache (16%), injection site reaction (15%), hyperglycemia (14%), hypertension (14%), cholelithiasis (14%). The rates of discontinuation due to treatment-related adverse reactions were 5% (5/101 patients) in the Somatuline[®] 120mg arm and 3% (3/103 patients) in the placebo arm.

About Somatuline[®]

The active substance in Somatuline[®] is lanreotide acetate, a somatostatin analogue that inhibits the secretion of several endocrine, exocrine and paracrine functions. It has been shown to be effective in inhibiting the secretion of GH and certain hormones secreted by the digestive system. Somatuline[®] is marketed as Somatuline[®] Depot[®] within the United States and as Somatuline[®] Autogel[®] in other countries where it has marketing authorization for the treatment of acromegaly or the symptomatic treatment of neuroendocrine tumors.

Somatuline[®] was initially developed and continues to be used for the treatment of acromegaly in many countries, including the United States, where it is indicated for the long-term treatment of patients with acromegaly who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy.

Somatuline[®] will be delivered via a newly approved in the US, ready-to-use, prefilled syringe which incorporates Safe'n'Sound^{®6} technology, including a retractable guard to help avoid accidental needle

⁵ "Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors", July 17th 2014 edition, N. Engl. J. Med. 2014; 371: 224-233

⁶ Safe'n'Sound is a registered trademark of Nemera La Verpillière SAS



sticks, and it is manufactured without latex or natural dry rubber. The new delivery device does not require reconstitution and is a low volume (0.5 mL) deep subcutaneous injection offering a streamlined process that supports full dose delivery.

Adverse Reactions

In the GEP-NET pivotal trial, the most common adverse reactions (incidence >10% and more common than placebo) in patients treated with Somatuline® vs placebo were abdominal pain (34% vs 24%), musculoskeletal pain (19% vs 13%), vomiting (19% vs 9%), headache (16% vs 11%), injection site reaction (15% vs 7%), hyperglycemia (14% vs 5%), hypertension (14% vs 5%), and cholelithiasis (14% vs 7%).

The product information should be consulted for a complete list of undesirable effects, warnings and precautions and contraindications for use.

About Ipsen

Ipsen is a global specialty-driven pharmaceutical company with total sales exceeding €1.2 billion in 2013. Ipsen's ambition is to become a leader in specialty healthcare solutions for targeted debilitating diseases. Its development strategy is supported by 3 franchises: neurology, endocrinology and uro-oncology. 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. In 2013, R&D expenditure totaled close to €260 million, representing more than 21% of Group sales. Moreover, Ipsen also has a significant presence in primary care. The Group has close to 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 Statements

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.

For further information:

Media

Didier Véron

Senior Vice-Président, Public Affairs
and Communication

Tel.: +33 (0)1 58 33 51 16

Fax: +33 (0)1 58 33 50 58

E-mail: didier.veron@ipsen.com

Brigitte Le Guennec

Corporate External Communication Manager

Tel.: +33 (0)1 58 33 51 17

Fax: +33 (0)1 58 33 50 58

E-mail : brigitte.le.guennec@ipsen.com

Financial Community

Stéphane Durant des Aulnois

Investor Relations Director

Tel.: +33 (0)1 58 33 60 09

Fax: +33 (0)1 58 33 50 63

E-mail: stephane.durant.des.aulnois@ipsen.com

Thomas Peny-Coblentz, CFA

Investor Relations Deputy Director

Tel.: +33 (0)1 58 33 56 36

Fax: +33 (0)1 58 33 50 63

E-mail: thomas.peny-coblentz@ipsen.com