

## Ipsen announces acceptance of filings for Somatuline<sup>®</sup> in the treatment of GEP-NETs<sup>1</sup> in the US with priority review

**FDA decision expected by early Q1 2015**

**Basking Ridge, NJ, September 1, 2014** – Ipsen N.A., an affiliate of Ipsen (Euronext: IPN; ADR: IPSEY) today announced that the U.S. Food and Drug Administration (FDA) has accepted and granted priority review of its supplemental New Drug Application (sNDA) for Somatuline<sup>®</sup> Depot<sup>®</sup> 120mg injection in the treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs). The FDA designates priority review status to drug candidates that have the potential to offer a significant improvement in treatment compared to currently approved options. A decision is expected in early Q1, 2015.

The regulatory submission was supported by the results of the investigational CLARINET<sup>®</sup> Phase III study, which demonstrated the antitumor effect of Somatuline<sup>®</sup> in the treatment of patients with GEP-NETs, and which was recently published in the July 17th issue of The New England Journal of Medicine<sup>2</sup>.

**Marc de Garidel, Chairman and Chief Executive Officer of Ipsen** stated: “We are pleased that the US regulatory authorities have accepted the filing for Somatuline<sup>®</sup> in the treatment of GEP-NETs and that the dossier has been granted priority review. We are excited about the potential benefits Somatuline<sup>®</sup> could bring to patients suffering from this debilitating disease”.

**Cynthia Schwalm, President and CEO of Ipsen North America** said “To date, somatostatin analogs are approved to manage symptoms of GEP NETs and are not approved as anti-tumor therapy. Somatuline<sup>®</sup> is the first and only somatostatin analog to demonstrate a statistically significant improvement in progression free survival in GEP NET in a large, multinational study clinical trial.”

The data from CLARINET<sup>®</sup> is investigational, as Somatuline<sup>®</sup> Depot<sup>®</sup> is not approved for the treatment of GEP-NETs. Somatuline<sup>®</sup> Depot<sup>®</sup> is currently approved in the US for the treatment of acromegaly.

### **About gastroenteropancreatic neuroendocrine tumors**

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are serious and rare types of cancer. They constitute a heterogeneous group of tumors most often arising from cells in the gastrointestinal tract and the pancreas; although rare, their incidence has been on the rise (4-6 fold increase in the last 30 years). They have the ability to secrete functional amines and peptides and based on the type and

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<sup>1</sup> Gastroenteropancreatic neuroendocrine tumors

<sup>2</sup> “Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors”, July 17th 2014 edition, N. Engl. J. Med. 2014; 371: 224-233



amount of these bioactive substances in circulation, they can or cannot result in an identifiable hormonal clinical syndrome. GEP-NETs can be clinically silent for long periods of time, delaying the diagnosis until late presentation with hormonal related symptoms or with symptoms related to tumor mass effect such as intestinal obstruction or abdominal pain.

### **About Somatuline<sup>®</sup> Depot in the United States**

In the United States, Somatuline<sup>®</sup> Depot 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<sup>®</sup> Depot is not indicated for the treatment of GEP-NETs.

The active substance in Somatuline<sup>®</sup> Depot is lanreotide acetate, a somatostatin analogue that inhibits the secretion of several endocrine, exocrine and paracrine amines and peptides.

### **Select Important Safety Information about Somatuline<sup>®</sup> Depot for Patients**

Somatuline<sup>®</sup> Depot may cause serious side effects including:

- Gallstones
- Changes in your blood sugar (high blood sugar or low blood sugar)
- Slow heart rate
- High blood pressure

The most common side effects of Somatuline<sup>®</sup> Depot include diarrhea, gallstones, stomach area (abdominal) pain, nausea, and pain, itching, or a lump at the injection site.

These are not all the possible side effects of Somatuline<sup>®</sup> Depot. Tell your doctor if you have any side effect that bothers you or that does not go away.

Before you receive Somatuline<sup>®</sup> Depot, talk to your doctor about:

All of your medical conditions, including:

- Gallbladder, thyroid, heart, kidney, or liver problems
- Diabetes
- Allergy to latex or natural dry rubber
- Pregnancy or plans to become pregnant
  - It is not known if Somatuline<sup>®</sup> Depot could harm your unborn baby
- Breast-feeding or plans to breast-feed
  - It is not known if Somatuline<sup>®</sup> Depot passes into breast milk

Any medicines (prescription and nonprescription) you are taking, including:

- Insulin or other diabetes medicines
- A cyclosporine (such as Gengraf<sup>™</sup>, Neoral<sup>®</sup>, or Sandimmune<sup>®</sup>)
- A medicine called bromocriptine (such as Parlodel<sup>®</sup>)
- Medicines that lower your heart rate (such as beta blockers)



While on Somatuline<sup>®</sup> Depot:

- Tell your doctor if you have sudden pain in your upper right stomach (abdominal) area or in your right shoulder or between your shoulder blades, or if you have yellowing of your skin and whites of your eyes, fever with chills, or nausea as these could be symptoms related to gallstones
- If you have diabetes, test your blood sugar as your doctor tells you to. Your doctor may change your dose of diabetes medicine especially when you first start receiving Somatuline<sup>®</sup> Depot or if your dose of Somatuline<sup>®</sup> Depot changes.
- Before each treatment, read the Patient Information that comes with each Somatuline<sup>®</sup> Depot package as there may be new information. Talk with your doctor about your medical condition or your treatment. Your doctor is your primary source of information about treatment.

Please see the Patient Information for Somatuline<sup>®</sup> Depot at [http://somatulinedepot.com/assets/files/fpo\\_patient\\_pi.pdf](http://somatulinedepot.com/assets/files/fpo_patient_pi.pdf)

### **Select Important Safety Information about Somatuline<sup>®</sup> Depot for Healthcare Professionals**

#### **Contraindications**

Somatuline<sup>®</sup> is contraindicated in patients with hypersensitivity to lanreotide or related peptides.

#### **Warnings and Precautions**

- Somatuline<sup>®</sup> may reduce gallbladder motility and lead to gallstone formation. Periodic monitoring may be needed
- Patients may experience hypoglycemia or hyperglycemia. Glucose level monitoring is recommended and antidiabetic treatment adjusted accordingly
- Somatuline<sup>®</sup> may decrease heart rate. In cardiac studies, the most common cardiac adverse reactions were sinus bradycardia, bradycardia, and hypertension. Dose adjustment of coadministered drugs that decrease heart rate may be necessary
- Somatuline<sup>®</sup> may decrease bioavailability of cyclosporine. Cyclosporine dose may need to be adjusted

#### **Adverse Reactions**

The most common adverse reactions (incidence >5%) were diarrhea (37%), cholelithiasis (20%), abdominal pain (19%), nausea (11%), injection-site reaction (9%), constipation (8%), flatulence (7%), headache (7%), arthralgia (7%), vomiting (7%), and loose stools (6%).

#### **Use in Special Populations**

Patients with moderate and severe renal impairment or moderate and severe hepatic impairment: Initial dose is 60 mg every 4 weeks.

Please see the full Prescribing Information for Somatuline<sup>®</sup> Depot at [http://somatulinedepot.com/pdf/pi\\_2013november.pdf](http://somatulinedepot.com/pdf/pi_2013november.pdf)

#### **About CLARINET<sup>®</sup>**



CLARINET<sup>®</sup> is an investigational, 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 (ENETS).

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<sup>®</sup> Autogel<sup>®</sup> 120 mg (n=101) or placebo (n=103). At enrollment, primary tumor locations were pancreas (44%), midgut (36%), hindgut (7%) and unknown (13%). Most patients had stable disease (96%) and were treatment-naïve (84%). Thirty percent of patients had a Ki67 of 3% to ≤10% (WHO grade 2) and 33% had an 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 or magnetic resonance imaging scans (12 to 24 weeks) were performed, followed by additional scans at 12- week intervals during the first year and 24-week intervals during the second year up to 96 weeks.

The data showed that placebo-treated patients had a median PFS of 18.0 months and 33.0% had not progressed or died at 96 weeks, whereas the median PFS for Somatuline<sup>®</sup> 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 antiproliferative effects of Somatuline<sup>®</sup> were observed in a large population of patients with grade G1 or G2 (World Health Organization classification) GEP-NETs, and independent of hepatic tumor volume (≤25% or >25%). Quality of life measures were not different between the Somatuline<sup>®</sup> and placebo groups. Safety data generated from the study are consistent with the known safety profile of Somatuline<sup>®</sup>.

### **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, visit [www.ipsen.com](http://www.ipsen.com).

### **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.

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