

## Ipsen receives positive CHMP opinion for approval of Xermelo<sup>®</sup> (telotristat ethyl), for the treatment of carcinoid syndrome diarrhea in patients inadequately controlled by somatostatin analogue therapy

- **Positive opinion based on the results of two randomized Phase 3 trials, TELESTAR and TELECAST**

**Paris (France), July 21, 2017** — 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), has adopted a positive opinion recommending the approval of Xermelo<sup>®</sup> (telotristat ethyl) 250 mg three times a day (tid) for the treatment of carcinoid syndrome diarrhea in combination with somatostatin analogue (SSA) therapy in adults inadequately controlled by SSA therapy. The CHMP positive opinion will now be reviewed by the European Commission (EC), which has the authority to approve medicines for use in the 28 countries of the European Union, as well as Norway, Liechtenstein and Iceland.

**David Meek, Chief Executive Officer of Ipsen**, said: *“The positive CHMP opinion for Xermelo<sup>®</sup> is an important milestone towards providing innovative solutions along every step of the treatment pathway for neuroendocrine tumors. Xermelo<sup>®</sup> is a novel treatment option and is the first oral tryptophan hydroxylase inhibitor, studied in combination with a somatostatin analog to demonstrate significant relief to patients and can contribute to an improved quality of life. We are very pleased to move closer to providing a new treatment option for European patients suffering from this debilitating condition.”*

*“The medical community is very pleased to have Xermelo<sup>®</sup> as a new therapeutic option for patients with carcinoid syndrome”,* said **Professor Juan Valle, University of Manchester and The Christie in Manchester, UK**. He added *“The positive safety and efficacy data of telotristat ethyl has meant that it has already been integrated in the majority of international guidelines including ENETS<sup>1</sup> guidelines reflecting the high level of unmet need in this condition”.*

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

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<sup>1</sup> European Neuroendocrine Tumor Society

### **About the TELESTAR Phase 3 Pivotal Trial**

The efficacy and safety of telotristat ethyl 250 mg taken tid were established in a 12-week double-blind, placebo-controlled, randomised, multicentre phase 3 trial. The study included a 36-week open-label extension period during which all patients were treated with a higher dose of telotristat ethyl. A total of 135 patients were recruited in 12 countries (AU, BE, CA, FR, DE, IL, IT, NL, ES, SE, UK, USA). The mean age was 64 years (range 37 to 88 years) and 52% were male. All patients had a well-differentiated metastatic neuroendocrine tumours with documented history of carcinoid syndrome, and were treated with stable-dose SSAs for  $\geq 3$  months before enrolment. Patients had an average of four or more bowel movements (BM) per day: at baseline, mean daily BM frequency averaged over the baseline period were 5.2 and 6.1 counts/day in the placebo and telotristat ethyl 250 mg groups, respectively. The study included a 12-week double-blind treatment (DBT) period, in which patients initially received placebo (n=45) or telotristat ethyl 250 mg (n=45) or a higher dose (telotristat ethyl 500 mg; n=45) three times daily. During the study, patients were allowed to use rescue medication (short-acting SSA therapy) and anti-diarrheals for symptomatic relief but were required to be on stable-dose of long-acting SSA therapy for the duration of the DBT period.

The primary endpoint was the mean change from baseline in daily BM frequency averaged over the 12-week double blind period. Estimated difference in BM frequency per day versus placebo averaged over 12 weeks was -0.81 for telotristat ethyl 250mg ( $p < 0.001$ ).

A substantially greater proportion of patients on telotristat ethyl 250 mg tid achieved a durable response, defined as at least a 30 percent reduction in daily bowel movements over at least half the days of the 12-week DBT period: 44 percent on telotristat ethyl, as compared to 20 percent on placebo ( $p < 0.040$ ). When the full effect of telotristat ethyl is observed (during the last 6 weeks of the DBT period) the proportion of responders with at least 30% BM reduction was 51% (23/45) in the 250 mg group versus 22% (10/45) in the placebo group (*post-hoc* analysis).

Telotristat ethyl significantly reduced the percent change from baseline in urinary 5-hydroxyindole acetic acid (u-5HIAA) versus placebo at week 12 ( $p < 0.001$ ).

### **About the TELECAST Phase 3 Trial**

The Phase 3 TELECAST study was designed similarly to TELESTAR study as a companion to this pivotal Phase 3 study to provide additional efficacy and safety information in patients with carcinoid syndrome.

A total of 76 patients were evaluated for efficacy. The mean age was 63 years (range 35 to 84 years) and 55% were male. All patients had well-differentiated metastatic neuroendocrine tumour with carcinoid syndrome. Most patients (92.1%) had fewer than 4 BM per day and all except 9 were treated by SSA therapy.

The primary endpoints were the percent change from Baseline in u5-HIAA at Week 12 and incidence of treatment emergent adverse events (TEAEs). The mean u5-HIAA excretion at baseline was 69.1 mg/24hours in the telotristat ethyl 250 mg tid group (n=17) and 84.8 mg/24hours in the placebo group (n=22). The percent change from baseline in u5-HIAA excretion at week 12 was +97.7% in the placebo group versus -33.2% in the telotristat ethyl 250 mg tid group.

Notably, 40% of patients in the telotristat ethyl 250 mg tid treatment arm achieved a  $\geq 30\%$  reduction in BM frequency for at least 50% of the days in the double-blind treatment period, while there were no responders in the placebo arm ( $p = 0.001$ ).

### **General safety information about Xermelo®**

In clinical trials, over 230 patients with carcinoid syndrome were treated with Xermelo®. The placebo-controlled safety analyses were focused on the integrated data from the 12-week placebo-controlled double-

blind periods from the two phase 3 randomized clinical trials. For this safety analysis, 71 patients received placebo and 70 patients received Xermelo<sup>®</sup> 250 mg three times daily. The most commonly reported adverse reactions in patients treated with telotristat ethyl were abdominal pain (26%), gamma-glutamyl transferase increased (11%) and fatigue (10%). They were generally of mild or moderate intensity. The most frequently reported adverse reaction leading to discontinuation of telotristat ethyl was abdominal pain in 7.1% of patients (5/70).

### **About carcinoid syndrome (CS)**

Well-differentiated neuroendocrine tumor (NET) is a relatively rare tumor type that arises from cells of the neuroendocrine system. Carcinoid syndrome (CS) occurs when well-differentiated NETs secrete large amounts of serotonin and other vasoactive products into the systemic circulation. Classically, symptoms associated with CS include cutaneous flushing, diarrhea, wheezing, abdominal pain, and in the long-term, valvular heart disease.

Somatostatin analogues (SSA) are the cornerstone of therapy for the relief of CS and tumor control. SSA inhibit the release of serotonin by NETs and have become first-line therapy for CS.

Due to the severe morbidity of CS and the lack of established treatment options, the population of patients with CS needing further control in addition to their SSA therapy is one with a high unmet medical need.

### **About Xermelo<sup>®</sup> (telotristat ethyl)**

Xermelo<sup>®</sup> is a novel, orally administered, inhibitor of the enzyme tryptophan hydroxylase (TPH). Through inhibition of TPH, the rate-limiting step in the synthesis of serotonin, Xermelo<sup>®</sup> was designed to reduce the production of serotonin within neuroendocrine tumors.

On 22 October 2014, Ipsen and Lexicon announced that they had entered into an exclusive licensing agreement for Ipsen to commercialize Xermelo<sup>®</sup> (telotristat ethyl) in all territories excluding the United States and Japan, where Lexicon retains the rights. On 28 February 2017, Lexicon received U.S. Food and Drug Administration (FDA) approval for Xermelo<sup>®</sup> as a first and only orally administered therapy for the treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.

### **About Ipsen**

Ipsen is a global specialty-driven biopharmaceutical group focused on innovation and specialty care. The group develops and commercializes innovative medicines in three key therapeutic areas - Oncology, Neurosciences and Rare Diseases. Its commitment to oncology is exemplified through its growing portfolio of key therapies for prostate cancer, neuroendocrine tumors, renal cell carcinoma and pancreatic cancer. Ipsen also has a well-established Consumer Healthcare business. With total sales close to €1.6 billion in 2016, Ipsen sells more than 20 drugs in over 115 countries, with a direct commercial presence in more than 30 countries. Ipsen's R&D is focused on its innovative and differentiated technological platforms located in the heart of the leading biotechnological and life sciences hubs (Paris-Saclay, France; Oxford, UK; Cambridge, US). The Group has about 5,100 employees worldwide. Ipsen is listed in Paris (Euronext: IPN) and in the United States through a Sponsored Level I American Depositary Receipt program (ADR: IPSEY). For more information on Ipsen, visit [www.ipsen.com](http://www.ipsen.com).

### **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 favorable 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 2016 Registration Document available on its website ([www.ipsen.com](http://www.ipsen.com)).

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