

Ipsen announces 16 abstract presentations of oncology portfolio at European Society of Medical Oncology congress

Paris (France), 4 September 2017 – Ipsen (Euronext: IPN; ADR: IPSEY) today announced that irinotecan liposome injection (Onivyde®), cabozantinib (Cabometyx®), lanreotide (Somatuline® Autogel® / Depot), telotristat ethyl (Xermelo®) and neuroendocrine tumors are the subject of 16 presentations at the European Society of Medical Oncology (ESMO 2017) congress. The meeting takes place in Madrid (Spain) September 8-12, 2017.

“Ipsen has its strongest presence in oncology at ESMO 2017 with 16 abstracts presenting clinical outcomes in pancreatic cancer, renal cell carcinoma, neuroendocrine tumors and carcinoid syndrome. Key highlights from the Ipsen oncology portfolio include new results from the CABOSUN study that investigated Cabometyx® in 1st line advanced renal cell carcinoma. The results have been selected as part of ESMO’s official program on Sunday September 10th,” **said Alexandre Lebeaut, MD, Executive Vice-President, R&D, Chief Scientific Officer, Ipsen.**

Ipsen and its partner Exelixis will host a IR / media meeting on September 10th at 6:45pm to present the latest developments related to cabozantinib (Cabometyx®) (Room Colon). Details about the conference call and the web conference (audio and video webcast) will be available at www.ipсен.com.

Abstracts on the following topics will be presented beginning Saturday, September 9, 2017 in IFEMA – Feria de Madrid:

Irinotecan liposome injection (Onivyde®) is featured in 2 abstracts:

Poster Display Session, September 9th 13:15-14:15 Hall 8

GASTROINTESTINAL TUMOURS, COLORECTAL

- 741P - Prognostic value of baseline neutrophil-to-lymphocyte ratio for predicting clinical outcome in metastatic pancreatic ductal adenocarcinoma (mPDAC) patients treated with liposomal irinotecan (nal-IRI) + 5-fluorouracil and leucovorin (5-FU/LV) vs 5-FU/LV alone

Presenter: R A Hubner (Manchester, England) [Ipsen-sponsored study]

- 70TiP - NIFE-Trial: Liposomal irinotecan (nal-IRI) plus 5-fluorouracil (5-FU) and leucovorin (LV) or gemcitabine plus cisplatin in advanced biliary-tract cancer - an open label, randomized, multicenter phase II trial of the AIO

Presenter: TJ Ettrich (Ulm, Germany) [Investigator-lead study]



Cabozantinib (Cabometyx®) is featured in 7 abstracts selected for oral presentation or poster sessions:

Proffered Paper Session, September 9th 09:15-10:45 Madrid Auditorium

GENITOURINARY TUMOURS, NON-PROSTATE

- 8460 - Final results of a phase I study of cabozantinib (Cabo) plus nivolumab (Nivo) and CaboNivo plus Ipilimumab (Ipi) in patients (pts) with metastatic urothelial carcinoma (mUC) and other genitourinary (GU) malignancies

Presenter: R Nadal (Bethesda, USA) [Investigator-lead study]

Poster session, September 10th 13:15-14:15 Hall 8

- 872P - Outcomes based on plasma biomarkers in METEOR, a randomized phase 3 trial of cabozantinib (C) vs everolimus (E) in advanced renal cell carcinoma (RCC)

Presenter: T Powles (London, UK) [Exelixis-sponsored study]

- 876P - Efficacy of cabozantinib (C) after PD-1/PD-L1 checkpoint inhibitors in metastatic Renal Cell Carcinoma (mRCC): the Gustave Roussy experience.

Presenter: L Derosa (Villejuif, France) [Investigator-lead study]

- 901P - Safety and efficacy of Cabozantinib for metastatic renal cell carcinoma (mRCC): real world data from an Italian Expanded Access Program (EAP)

Presenter: G Procopio (Milan, Italy) [Investigator-lead study]

- 912P - Cabozantinib for the treatment of patients with metastatic variant histology renal cell carcinoma (vhRCC): a retrospective study

Presenter: M T Campbell (Houston, USA) [Investigator-lead study]

- 927TiP - Cabozantinib in patients with advanced penile squamous cell carcinoma (PSCC): the open-label, single-arm, single-center, phase 2, CaboPen trial

Presenter: A Necchi (Milan, Italy) [Investigator-lead study]

Poster Discussion Session, September 10th, 14:45-16:15, Cordoba Auditorium

- LBA38 - Progression-free survival (PFS) by independent review and updated overall survival (OS) results from Alliance A031203 trial (CABOSUN): cabozantinib versus sunitinib as initial targeted therapy for patients (pts) with metastatic renal cell carcinoma (mRCC)



Presenter: TK Choueiri (Boston, USA) [Investigator-lead study]

Lanreotide (Somatuline® Autogel®) is featured in 2 abstracts:

Poster session, September 10th, 13:15 - 14:15, Hall 8

- 451P – Final analysis of time to subsequent disease progression/death in patients with metastatic enteropancreatic neuroendocrine tumours progressing under placebo and switched to lanreotide Autogel/Depot 120 mg in the CLARINET open-label extension
Presenter: Jarosław B. Ćwikła (Olsztyn, Poland) [Ipsen-sponsored study]
- 460P – Elevated levels of 5-HIAA and CgA in Patients with Pancreatic Neuroendocrine Tumors (PanNETs) from the CLARINET Study
Presenter: Alexandria T. Phan (Albuquerque, United States of America) [Ipsen-sponsored study]

Neuroendocrine tumors clinical research is featured in 1 abstract:

Poster session, September 10th, 13:15 - 14:15, Hall 8

- 463P – Plasma Protein Fingerprinting for the Diagnosis of Small Intestinal Neuroendocrine Tumors: The Nordic NET Biomarker Group EXPLAIN Study
Presenter: Magnus M. Kjellman (Stockholm, Sweden) [Ipsen-sponsored study]

Telotristat ethyl (Xermelo®) is featured in 4 posters

Poster session, September 10th, 13:15 - 14:15, Hall 8

- 443P – Identifying Symptom and Quality of Life Improvements in Patients with Carcinoid Syndrome Treated with Telotristat Ethyl: Qualitative Patient Exit Interviews from the TELESTAR Trial
Presenter: Florence Marteau ([Ipsen] Boulogne-Billancourt, France) [Ipsen-sponsored analysis]
- 445P - Relationship between Symptoms and Health-Related Quality of Life Benefits in Patients with Carcinoid Syndrome: Post-Hoc Analyses from TELESTAR
Presenter: Marianne Pavel (Berlin, Germany) [Ipsen-sponsored analysis]
- 442P – Long-term Survival of Patients With Carcinoid Syndrome in Clinical Trials of Telotristat Ethyl
Presenter: Pablo Lapuerta ([Lexicon] The Woodlands, USA) [Lexicon-sponsored study]

Poster discussion session, September 11th, 11:00 - 12:00, Alicante Auditorium

- 440PD – Efficacy and Safety of Telotristat Ethyl in Patients With Carcinoid Syndrome Inadequately Controlled by Somatostatin Analogs: Analysis of the Completed TELESTAR Extension Period



Presenter: Dieter Hörsch (Bad Berka, Germany) [Lexicon-sponsored study]

Nota bene: Approved indications for products vary by country and not all indications are available in every country. The product safety and efficacy profiles have not yet been established outside the approved indications.

ABOUT ONIVYDE®

ONIVYDE® is a novel encapsulation of irinotecan in a long-circulating liposome. This long-circulating liposomal form is designed to increase length of tumor exposure to both irinotecan and its active metabolite, SN- 38. ONIVYDE® is approved by the U.S. FDA in combination with fluorouracil and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy. For full prescribing information, including Boxed WARNING, please visit www.ONIVYDE.com.

INDICATION

ONIVYDE® (irinotecan liposome injection) is indicated, in combination with fluorouracil (5-FU) and leucovorin (LV), for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy. Limitation of Use: ONIVYDE® is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

IMPORTANT SAFETY INFORMATION - UNITED STATES

WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA

Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE®. Severe or life threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE® in combination with fluorouracil (5-FU) and leucovorin (LV). Withhold ONIVYDE® for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment.

Severe diarrhea occurred in 13% of patients receiving ONIVYDE® in combination with 5- FU/LV. Do not administer ONIVYDE® to patients with bowel obstruction. Withhold ONIVYDE® for diarrhea of Grade 2-4 severity.

CONTRAINDICATION

ONIVYDE® is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE® or irinotecan HCl.

WARNINGS AND PRECAUTIONS

Severe Neutropenia

ONIVYDE® can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In a clinical study, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE®, occurring in 1/117 patients in the ONIVYDE®/5-FU/LV arm and 1/147 patients receiving ONIVYDE® as a single agent. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE®/5-FU/LV vs 2% of patients receiving 5-FU/LV. Grade 3/4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE®/5-FU/LV, and did not occur in patients receiving 5-FU/LV.

In patients receiving ONIVYDE®/5-FU/LV, the incidence of Grade 3/4 neutropenia was higher among Asian (18/33 [55%]) vs White patients (13/73 [18%]). Neutropenic fever/neutropenic sepsis was reported in 6% of Asian vs 1% of White patients.

Severe Diarrhea

ONIVYDE® can cause severe and life-threatening diarrhea. Do not administer ONIVYDE® to patients with bowel obstruction. Severe and life-threatening late-onset (onset > 24 hours after chemotherapy) and early-



onset diarrhea (onset \leq 24 hours after chemotherapy, sometimes with other symptoms of cholinergic reaction) were observed. An individual patient may experience both early- and late-onset diarrhea.

In a clinical study, Grade 3/4 diarrhea occurred in 13% of patients receiving ONIVYDE®/5-FU/LV vs 4% receiving 5-FU/LV. Grade 3/4 late-onset diarrhea occurred in 9% of patients receiving ONIVYDE®/5-FU/LV vs 4% in patients receiving 5-FU/LV; the incidences of early-onset diarrhea were 3% and no Grade 3/4 incidences, respectively. Of patients receiving ONIVYDE®/5-FU/LV, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea.

Interstitial Lung Disease (ILD)

Irinotecan HCl can cause severe and fatal ILD. Withhold ONIVYDE® in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE® in patients with a confirmed diagnosis of ILD.

Severe Hypersensitivity Reactions

Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE® in patients who experience a severe hypersensitivity reaction.

Embryo-Fetal Toxicity

Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE®, ONIVYDE® can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during and for 1 month after ONIVYDE® treatment.

ADVERSE REACTIONS

- The most common (\geq 20%) adverse reactions in which patients receiving ONIVYDE®/5-FU/LV experienced a \geq 5% higher incidence of any Grade vs the 5-FU/LV arm, were diarrhea (any 59%, 26%; severe 13%, 4%) (early diarrhea [any 30%, 15%; severe 3%, 0%], late diarrhea [any 43%, 17%; severe 9%, 4%]), fatigue/asthenia (any 56%, 43%; severe 21%, 10%), vomiting (any 52%, 26%; severe 11%, 3%), nausea (any 51%, 34%; severe 8%, 4%), decreased appetite (any 44%, 32%; severe 4%, 2%), stomatitis (any 32%, 12%; severe 4%, 1%), pyrexia (any 23%, 11%; severe 2%, 1%).
- Of less common (< 20%) adverse reactions, patients receiving ONIVYDE®/5-FU/LV who experienced Grade 3/4 adverse reactions at a \geq 2% higher incidence of Grade 3/4 toxicity vs the 5-FU/LV arm, respectively, were sepsis (3%, 1%), neutropenic fever/neutropenic sepsis (3%, 0%), gastroenteritis (3%, 0%), intravenous catheter-related infection (3%, 0%), weight loss (2%, 0%), and dehydration (4%, 2%).
- The laboratory abnormalities in which patients receiving ONIVYDE®/5-FU/LV experienced a \geq 5% higher incidence vs the 5-FU/LV arm, were anemia (any 97%, 86%; severe 6%, 5%), lymphopenia (any 81%, 75%; severe 27%, 17%), neutropenia (any 52%, 6%; severe 20%, 2%), thrombocytopenia (any 41%, 33%; severe 2%, 0%), increased alanine aminotransferase (any 51%, 37%; severe 6%, 1%), hypoalbuminemia (any 43%, 30%; severe 2%, 0%), hypomagnesemia (any 35%, 21%; severe 0%, 0%), hypokalemia (any 32%, 19%; severe 2%, 2%), hypocalcemia (any 32%, 20%; severe 1%, 0%), hypophosphatemia (any 29%, 18%; severe 4%, 1%), hyponatremia (any 27%, 12%; severe 5%, 3%), increased creatinine (any 18%, 13%; severe 0%, 0%).
- ONIVYDE® can cause cholinergic reactions manifesting as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis, and intestinal hyperperistalsis with abdominal cramping and early-onset diarrhea. Grade 1/2 cholinergic symptoms other than early diarrhea occurred in 12 (4.5%) ONIVYDE®-treated patients.



- Infusion reactions, consisting of rash, urticaria, periorbital edema, or pruritus, occurring on the day of ONIVYDE® administration were reported in 3% of patients receiving ONIVYDE® or ONIVYDE®/5-FU/LV.
- The most common serious adverse reactions ($\geq 2\%$) of ONIVYDE® were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

DRUG INTERACTIONS

Avoid the use of strong CYP3A4 inducers, if possible, and substitute non-enzyme-inducing therapies ≥ 2 weeks prior to initiation of ONIVYDE®. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors, if possible, and discontinue strong CYP3A4 inhibitors ≥ 1 week prior to starting therapy.

USE IN SPECIFIC POPULATIONS

Pregnancy and Reproductive Potential

Advise pregnant women of the potential risk to a fetus. Advise males with female partners of reproductive potential to use effective contraception during and for 4 months after ONIVYDE® treatment.

Lactation

Advise nursing women not to breastfeed during and for 1 month after ONIVYDE® treatment.

Pediatric

Safety and effectiveness of ONIVYDE® have not been established in pediatric patients.

DOSAGE AND ADMINISTRATION

The recommended dose of ONIVYDE® is 70 mg/m² intravenous (IV) infusion over 90 minutes every 2 weeks, administered prior to LV and 5-FU. The recommended starting dose of ONIVYDE® in patients known to be homozygous for the UGT1A1*28 allele is 50 mg/m² administered by IV infusion over 90 minutes. There is no recommended dose of ONIVYDE® for patients with serum bilirubin above the upper limit of normal. Premedicate with a corticosteroid and an anti-emetic 30 minutes prior to ONIVYDE®. Withhold ONIVYDE® for Grade 3/4 adverse reactions. Resume ONIVYDE® with reduced dose once adverse reaction recovered to \leq Grade 1. Discontinue ONIVYDE® in patients who experience a severe hypersensitivity reaction and in patients with a confirmed diagnosis of ILD.

Do not substitute ONIVYDE® for other drugs containing irinotecan HCl.

Please see full U.S. [Prescribing Information](#) for ONIVYDE®.

ABOUT CABOMETYX®

Cabometyx® is the tablet formulation of cabozantinib. Its targets include MET, AXL, and VEGFR receptors in tumor cells. In preclinical models, cabozantinib has been shown to inhibit the activity of these receptors, which are involved in normal cellular function and pathologic processes such as tumor angiogenesis, invasiveness, metastasis and drug resistance.



Cabozantinib is the first and only monotherapy to demonstrate statistically significant superiority in overall survival, progression-free survival, and objective response rate compared with everolimus in patients with RCC who have failed previous treatment with anti-angiogenic therapy.^{1 2}

Indications: CABOMETYX® is indicated for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy.

Dosage and Administration: The recommended dose of CABOMETYX® is 60 mg once daily. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of CABOMETYX® therapy. For dose modification, please refer to full SmPC. CABOMETYX® is for oral use. The tablets should be swallowed whole and not crushed. Patients should be instructed to not eat anything for at least 2 hours before through 1 hour after taking CABOMETYX®.

Contraindications: Hypersensitivity to the active substance or to any of the excipients listed in the SmPC.

Special warnings and precautions for use: As most events can occur early in the course of treatment, the physician should evaluate the patient closely during the first eight weeks of treatment to determine if dose modifications are warranted. Events that generally have early onset include hypocalcaemia, hypokalaemia, thrombocytopenia, hypertension, palmarplantar erythrodysesthesia syndrome (PPES), proteinuria, and gastrointestinal (GI) events (abdominal pain, mucosal inflammation, constipation, diarrhoea, vomiting). Dose reductions and dose interruptions due to an AE occurred in 59.8% and 70%, respectively, of cabozantinib-treated patients in the pivotal clinical trial. Two dose reductions were required in 19.3% of patients. The median time to first dose reduction was 55 days, and to first dose interruption was 38 days. Perforations and fistulas: Serious gastrointestinal perforations and fistulas, sometimes fatal, have been observed with cabozantinib. Patients who have inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, peritonitis, diverticulitis, or appendicitis), have tumour infiltration in the GI tract, or have complications from prior GI surgery (particularly when associated with delayed or incomplete healing) should be carefully evaluated before initiating cabozantinib therapy and subsequently they should be monitored closely for symptoms of perforations and fistulas including abscesses. Persistent or recurring diarrhoea while on treatment may be a risk factor for the development of anal fistula. Cabozantinib should be discontinued in patients who experience a GI perforation or a fistula that cannot be adequately managed.

Thromboembolic events: Events of venous thromboembolism, including pulmonary embolism, and events of arterial thromboembolism have been observed with cabozantinib. Cabozantinib should be used with caution in patients who are at risk for, or who have a history of, these events. Cabozantinib should be discontinued in patients who develop an acute myocardial infarction or any other clinically significant arterial thromboembolic complication.

¹ Choueiri TK, Escudier B, Powles T et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from randomised, open-label, phase 3 trial. *Lancet Oncol.* 2016; 17(7):917-27

² Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med.* 2015 Nov;373:1814-1823.

Haemorrhage: Severe haemorrhage has been observed with cabozantinib. Patients who have a history of severe bleeding prior to treatment initiation should be carefully evaluated before initiating cabozantinib therapy. Cabozantinib should not be administered to patients that have or are at risk for severe haemorrhage.

Wound complications: Wound complications have been observed with cabozantinib. Cabozantinib treatment should be stopped at least 28 days prior to scheduled surgery, including dental surgery, if possible. The decision to resume cabozantinib therapy after surgery should be based on clinical judgment of adequate wound healing. Cabozantinib should be discontinued in patients with wound healing complications requiring medical intervention.

Hypertension: Hypertension has been observed with cabozantinib. Blood pressure should be well-controlled prior to initiating cabozantinib. During treatment with cabozantinib, all patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensives, the cabozantinib dose should be reduced. Cabozantinib should be discontinued if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of cabozantinib. In case of hypertensive crisis, cabozantinib should be discontinued.

Palmar-plantar erythrodysesthesia syndrome: Palmar-plantar erythrodysesthesia syndrome (PPES) has been observed with cabozantinib. When PPES is severe, interruption of treatment with cabozantinib should be considered. Cabozantinib should be restarted with a lower dose when PPES has been resolved to grade 1.

Proteinuria: Proteinuria has been observed with cabozantinib. Urine protein should be monitored regularly during cabozantinib treatment. Cabozantinib should be discontinued in patients who develop nephrotic syndrome.

Reversible posterior leukoencephalopathy syndrome: Reversible Posterior Leukoencephalopathy Syndrome (RPLS), also known as Posterior Reversible Encephalopathy Syndrome (PRES), has been observed with cabozantinib. This syndrome should be considered in any patient presenting with multiple symptoms, including seizures, headache, visual disturbances, confusion or altered mental function. Cabozantinib treatment should be discontinued in patients with RPLS.

Prolongation of QT interval

Cabozantinib should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using cabozantinib, periodic monitoring with on-treatment ECGs and electrolytes (serum calcium, potassium, and magnesium) should be considered.

Interactions: CYP3A4 inducers and inhibitors: cabozantinib is a CYP3A4 substrate. Concurrent administration of cabozantinib with the strong CYP3A4 inhibitor ketoconazole resulted in an increase in cabozantinib plasma exposure. Caution is required when administering cabozantinib with agents that are strong CYP3A4 inhibitors. Concurrent administration of cabozantinib with the strong CYP3A4 inducer rifampicin resulted in a decrease in cabozantinib plasma exposure. Therefore, chronic administration of agents that are strong CYP3A4 inducers with cabozantinib should be avoided. P-glycoprotein substrates: Cabozantinib was an inhibitor but not a substrate, of P-glycoprotein (P-gp) transport activities in a bi-directional assay system using MDCK-MDR1 cells. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. Subjects should be cautioned regarding taking a P-gp substrate while receiving cabozantinib. MRP2 inhibitors: Administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations. Therefore, concomitant use of MRP2 inhibitors should be approached with caution. Bile salt-sequestering agents: Bile salt-sequestering agents may interact with cabozantinib and may impact absorption (or reabsorption) resulting in potentially decreased exposure. The clinical significance of these

potential interactions is unknown. Excipient related warnings: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Pregnancy and lactation: Avoid pregnancy, use effective methods of contraception and discontinue breastfeeding during treatment with cabozantinib, and for at least 4 months after completing therapy.

Drive and use machines: Caution is recommended

Undesirable effects:

The most common serious adverse reactions associated with cabozantinib are abdominal pain (3%), pleural effusion (3%), diarrhoea (2%), and nausea (2%). The most frequent adverse reactions of any grade (experienced by at least 25% of patients) included diarrhoea (74%), fatigue (56%), nausea (50%), decreased appetite (46%), palmar-plantar erythrodysaesthesia syndrome (PPES) (42%), hypertension (37%), vomiting (32%), weight decreased (31%), and constipation (25%). Other very common adverse reactions: anemia, hypophosphataemia, hypoalbuminaemia, hypomagnesaemia, hyponatraemia, hypokalaemia, hyperkalaemia, hypocalcaemia, hyperbilirubinemia, dysgeusia, headache, dizziness, dysphonia, dyspnea, cough, stomatitis, abdominal pain, dyspepsia, rash, dry skin, muscle spasms, arthralgia, proteinuria, mucosal inflammation, serum ALT, AST, and ALP increased, creatinine increased, triglycerides increased, hyperglycaemia, hypoglycaemia, lymphopenia, neutropenia, thrombocytopenia, GGT increased, amylase increased, blood cholesterol increased, lipase increased

For all common and uncommon adverse reactions, please refer to full SmPC. For more information, see the regularly updated registered product information on the European Medicine Agency www.ema.europa.eu

ABOUT SOMATULINE®

Somatuline® Autogel® / Depot® is made of the active substance lanreotide, which is a somatostatin analogue that inhibits the secretion of growth hormone and certain hormones secreted by the digestive system.

The main indications of Somatuline® and Somatuline® Autogel® are the following:

- Treatment of acromegaly when circulating levels of growth hormone and/or Insulin-like Growth Factor-1 remain abnormal after surgery and/or radiotherapy, or in patients who otherwise require medical treatment.
- Treatment of symptoms associated with carcinoid syndrome related to neuroendocrine tumors (ex-US).
- Anti-proliferative treatment of gastroenteropancreatic neuroendocrine tumors.

IMPORTANT SAFETY INFORMATION -

Contraindications:

Somatuline® is contraindicated in patients with hypersensitivity to lanreotide. Allergic reactions (including angioedema and anaphylaxis) have been reported following administration of lanreotide.

Warnings and Precautions:

- Cholelithiasis and Gallbladder Sludge: Somatuline may reduce gallbladder motility and lead to gallstone formation. Periodic monitoring may be needed.
- Hypoglycemia or Hyperglycemia: Pharmacological studies show that Somatuline®, like somatostatin and other somatostatin analogs, inhibits the secretion of insulin and glucagon. Blood glucose levels should be monitored when Somatuline treatment is initiated, or when the dose is altered, and antidiabetic treatment should be adjusted accordingly.

- **Cardiac Abnormalities:** Somatuline may decrease heart rate. In 81 patients with baseline heart rates of ≥ 60 beats per minute (bpm) treated with Somatuline in the GEPNETs clinical trial, the incidence of heart rate < 60 bpm was 23% (19/81) with Somatuline vs 16% (15/94) with placebo; 10 patients (12%) had documented heart rates < 60 bpm on more than one visit. The incidence of documented episodes of heart rate < 50 bpm or bradycardia reported as an adverse event was 1% in each treatment group. Initiate appropriate medical management in patients who develop symptomatic bradycardia.

In patients without underlying cardiac disease, Somatuline[®] may lead to a decrease in heart rate without necessarily reaching the threshold of bradycardia. In patients suffering from cardiac disorders prior to treatment, sinus bradycardia may occur. Care should be taken when initiating treatment in patients with bradycardia.

- **Drug Interactions:** The pharmacological gastrointestinal effects of Somatuline[®] may reduce the intestinal absorption of concomitant drugs. Concomitant administration of Somatuline[®] may decrease the relative bioavailability of cyclosporine and may necessitate the adjustment of cyclosporine dose to maintain therapeutic levels.

Adverse Reactions:

In the overall pooled safety studies in acromegaly, the most commonly reported adverse reactions reported by $> 5\%$ of patients who received Somatuline[®] (N=416 patients) were gastrointestinal disorders (diarrhea, abdominal pain, nausea, constipation, flatulence, vomiting, loose stools), cholelithiasis and injection site 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%).

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reaction via the national reporting system.

Please see the full Prescribing Information for Somatuline[®] by accessing the following [link](#).

ABOUT XERMELO[®] (TELOTRISTAT ETHYL)

Xermelo[®] 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[®] 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[®] (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[®] 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.

On 20 July 2017, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Xermelo, intended for the treatment of carcinoid syndrome diarrhoea in combination with a somatostatin analogue.



Detailed recommendations for the use of this product will be described in the summary of product characteristics (SmPC), which will be published in the European public assessment report (EPAR) and made available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

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® 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 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.ipсен.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 2016 Registration Document available on its website (www.ipsen.com).

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