PRESS RELEASE

Ipsen announces U.S. FDA submission acceptance of its supplemental New Drug Application for Onivyde regimen in first-line metastatic pancreatic ductal adenocarcinoma

- Supplemental New Drug Application (sNDA) submission based on the NAPOLI 3 Phase III trial[1]
- Approval would represent expansion of treatment options in an aggressive and difficult-to-treat cancer with few treatment options currently available

PARIS, FRANCE, 14 June 2023 – Ipsen (Euronext: IPN; ADR: IPSEY) today announced that the U.S. Food and Drug Administration (FDA) has accepted its supplemental new drug application (sNDA) Onivyde® (irinotecan liposome injection) plus 5 fluorouracil/leucovorin and oxaliplatin (NALIRIFOX regimen) as a potential first-line treatment for metastatic pancreatic ductal adenocarcinoma (mPDAC). The review is based on positive results from the pivotal Phase III NAPOLI 3 trial, in which the Onivyde regimen demonstrated a statistically significant improvement in overall survival (OS) and progression-free survival (PFS), compared to nab-paclitaxel plus gemcitabine, with a safety profile consistent with the profiles of the treatment components. These results were presented at the January 2023 American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI).

“PDAC is a devastating disease in need of additional treatment options. The FDA’s decision to accept the sNDA for this Onivyde-based regimen in treatment-naïve patients with metastatic disease represents an important milestone in the potential treatment of this complex form of cancer,” said Howard Mayer, Executive Vice President and Head of Research and Development at Ipsen. “We’re committed to developing therapies which have the potential to make a meaningful difference to the lives of people living with cancer and look forward to working with FDA as they review this application.”

The FDA provided a Prescription Drug User Fee Act goal date of 13 February 2024 for review of Ipsen’s application. In 2020, the FDA granted Ipsen Fast Track designation for Onivyde as a first-line combination treatment for mPDAC. The FDA’s Fast Track program facilitates the development and expedites the review of medicines that treat serious conditions and have the potential to address an unmet medical need.

NAPOLI 3 data, as presented at ASCO GI 2023

- Trial met its primary endpoint of OS, showing patients in the NALIRIFOX group had a statistically significant improvement in median OS of 11.1 months, versus 9.2 months in the nab-paclitaxel and gemcitabine group (HR 0.83 [95% CI 0.70–0.99]; p=0.04). At 12 months, the OS rate for the NALIRIFOX group was 45.6%, and for the nab-paclitaxel and gemcitabine group it was 39.5%. At 18 months, the OS rate was 26.2% for the NALIRIFOX group, and 19.3% for the nab-paclitaxel and gemcitabine group.[1]
- Trial met its secondary endpoint showing patients treated with NALIRIFOX had a statistically significant improvement in median PFS of 7.4 months versus 5.6 months for nab-paclitaxel and gemcitabine (HR 0.69 [95% CI 0.58–0.83]; p=0.0001).**Error! Bookmark not defined.**
- The objective response rate was 41.8% (36.8%-46.9%; 95% CI) for patients treated with the NALIRIFOX regimen versus 36.2% (31.4%-41.2%; 95% CI) for patients treated with nab-paclitaxel and gemcitabine.**Error! Bookmark not defined.**

- The safety profile of NALIRIFOX was consistent with the profiles of the treatment components. The most common Grade 3/4 treatment-emergent adverse events with more than 10% frequency in patients receiving NALIRIFOX versus nab-paclitaxel and gemcitabine included diarrhea (20.3% vs 4.5%), nausea (11.9% vs 2.6%), hypokalemia (15.1% vs 4.0%), anemia (10.5% vs 17.4%) and neutropenia (14.1% vs 24.5%).**Error! Bookmark not defined.**

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About the NAPOLI 3 trial Error! Bookmark not defined.
NAPOLI 3 is a randomized, open-label Phase III trial of an investigational Onivyde treatment regimen (NALIRIFOX) in patients who have not previously received chemotherapy for mPDAC. NAPOLI 3 enrolled 770 patients across 205 trial site locations in 18 countries. Patients were randomized to receive Onivyde plus 5 fluorouracil/leucovorin and oxaliplatin (NALIRIFOX regimen; n=383) twice in a month (days 1 and 15 of 28-day cycle) compared to an injection of nab-paclitaxel and gemcitabine (n=387) administered three times a month (days 1, 8, 15 of a 28-day cycle).

About Onivyde
Onivyde is a cancer medicine that blocks an enzyme called topoisomerase I, which is involved in copying cell DNA needed to make new cells. By blocking the enzyme, cancer cells are prevented from multiplying and eventually die. In Onivyde, irinotecan is enclosed in tiny fat particles called liposomes, which accumulate in the tumor and release slowly over time.

Onivyde is currently approved in most major markets including the U.S., the E.U. and Asia in combination with fluorouracil (5-FU) and leucovorin (LV) for the treatment of patients with mPDAC after disease progression following gemcitabine-based therapy. Onivyde is not indicated as a single agent for the treatment of patients with mPDAC.

Ipsen has exclusive commercialization rights for the current and potential future indications for Onivyde in the U.S. Servier, an independent pharmaceutical company with an international presence in 150 countries, is responsible for the commercialization of Onivyde outside of the U.S. and Taiwan. PharmaEngine is a commercial stage oncology company headquartered in Taipei and is responsible for the commercialization of Onivyde in Taiwan.

About PDAC
PDAC is the most common type of cancer that forms in the pancreas with approximately 60,000 people diagnosed in the U.S. each year and nearly 500,000 people globally.[2,3] Since there are no specific symptoms in the early stages, PDAC is often detected late and after the disease has spread to other parts of the body (metastatic or stage IV).[4] Even in later stages, weight loss, abdominal pain and jaundice are the most common symptoms making PDAC difficult to detect.[5] Despite significant advances in cancer treatments since the 1970s, no treatment options for PDAC significantly extend life.[4] Currently, fewer than 20% of people diagnosed with PDAC survive longer than one year and, overall, pancreatic cancer has the lowest five-year survival rate of all cancer types globally and in the U.S.[2,3]

U.S. IMPORTANT SAFETY INFORMATION

BOXED WARNINGS: 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 5-FU and 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. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity.

CONTRAINDICATION
Onivyde is contraindicated in patients who have experienced a severe hypersensitivity reaction to Onivyde or irinotecan hydrochloride.

Warnings and precautions

Severe neutropenia: **see boxed WARNING**. 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: **see boxed WARNING**. Severe and life-threatening late-onset (onset >24 hours after chemotherapy [9%]) and early-onset diarrhea (onset ≤24 hours after chemotherapy [3%], sometimes with other symptoms of cholinergic reaction) were observed.

Interstitial lung disease (ILD): Irinotecan HCl can cause severe and fatal ILD. Withhold Onivyde 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: Onivyde can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during and for 1 month after Onivyde treatment.

Adverse reactions

- The most common adverse reactions (≥20%) were diarrhea (59%), fatigue/asthenia (56%), vomiting (52%), nausea (51%), decreased appetite (44%), stomatitis (32%), and pyrexia (23%)
- The most common Grade 3/4 adverse reactions (≥10%) were diarrhea (13%), fatigue/asthenia (21%), and vomiting (11%).
- Adverse reactions led to permanent discontinuation of Onivyde in 11% of patients receiving Onivyde/5- FU/LV; the most frequent adverse reactions resulting in discontinuation of Onivyde were diarrhea, vomiting, and sepsis.
- Dose reductions of Onivyde for adverse reactions occurred in 33% of patients receiving Onivyde/5 FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia.
- Onivyde was withheld or delayed for adverse reactions in 62% of patients receiving Onivyde/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia.
- The most common laboratory abnormalities (≥20%) were anemia (97%), lymphopenia (81%), neutropenia (52%), increased ALT (51%), hypoalbuminemia (43%), thrombocytopenia (41%), hypomagnesemia (35%), hypokalemia (32%), hypocalcemia (32%), hypophosphatemia (29%), and hyponatremia (27%).

Drug interactions

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

Special populations

- Pregnancy and Reproductive Potential: See WARNINGS & PRECAUTIONS. Advise males with female partners of reproductive potential to use condoms during and for 4 months after Onivyde treatment.
- Lactation: Advise nursing women not to breastfeed during and for 1 month after Onivyde treatment.

Please see full U.S. **Prescribing Information** including Boxed WARNING for Onivyde.

About Ipsen

Ipsen is a global, mid-sized biopharmaceutical company focused on transformative medicines in Oncology, Rare Disease and Neuroscience. With total sales of €3.0bn in FY 2022, Ipsen sells medicines in over 100 countries. Alongside its external-innovation strategy, the Company's research and development efforts are focused on its innovative and differentiated technological platforms located in the heart of leading biotechnological and life-science hubs: Paris-Saclay, France; Oxford, U.K.; Cambridge, U.S.; Shanghai, China. Ipsen has around 5,400 colleagues worldwide and 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

Ipsen's forward-looking statements

The forward-looking statements, objectives and targets contained herein are based on Ipsen'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 Ipsen'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 Ipsen'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 Ipsen. 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 medicine 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. Ipsen must face or might face competition from generic medicine 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 Ipsen may fail to achieve its objectives and be forced to abandon its efforts with regards to a medicine in which it has invested significant sums. Therefore, Ipsen cannot be certain that favorable results obtained during preclinical 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 medicine concerned. There can be no guarantees a medicine will receive the necessary regulatory approvals or that the medicine 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

healthcare legislation; global trends toward healthcare cost containment; technological advances, new medicine and patents attained by competitors; challenges inherent in new-medicine development, including obtaining regulatory approval; Ipsen'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 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 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. 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 Universal Registration Document, available on **ipsen.com**

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[1] 1. Wainberg, Z.A et al. NAPOLI-3: A Randomized, Open-label Phase 3 Study of Liposomal Irinotecan + 5-fluorouracil/leucovorin + Oxaliplatin (NALIRIFOX) versus Nab-paclitaxel + Gemcitabine in Treatment-naïve Patients with Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC). Presented at ASCO Gastrointestinal Cancers Symposium, 2023 January 19-21; San Francisco, California.
[2] https://seer.cancer.gov/statfacts/html/pancreas.html
[3] https://www.cancer.net/cancer-types/pancreatic-cancer/statistics
[4] Orth, M., Metzger, P., Gerum, S. et al. Pancreatic ductal adenocarcinoma: biological hallmarks, current status, and future perspectives of combined modality treatment approaches. Radiat Oncol 14, 141 (2019). https://doi.org/10.1186/s13014-019-1345-6
[5] https://www.cancer.org/cancer/pancreatic-cancer/detection-diagnosis-staging/signs-and-symptoms.html