

Ipsen's Onivyde® regimen, a potential new standard-of-care first-line therapy in metastatic pancreatic adenocarcinoma, approved by FDA

- » Approval based on Phase III NAPOLI 3 clinical trial in which Onivyde® regimen (NALIRIFOX) demonstrated statistically significant superiority and clinically meaningful improvements in overall survival and progression-free survival versus nab-paclitaxel and gemcitabine¹
- » NAPOLI 3 represents the first positive Phase III trial in first-line metastatic pancreatic adenocarcinoma (mPDAC) to demonstrate superior overall survival versus the currently approved regimen of nab-paclitaxel and gemcitabine¹
- » Onivyde is the only FDA-approved treatment regimen to demonstrate efficacy in two Phase III trials across lines of therapy in mPDAC^{1,2}

PARIS, FRANCE, 13 February 2024 - Ipsen (Euronext: IPN; ADR: IPSEY) announced today that the U.S. Food and Drug Administration (FDA) has approved the supplemental new drug application for Onivyde® (irinotecan liposome injection) plus oxaliplatin, fluorouracil and leucovorin (NALIRIFOX) as a first-line treatment in adults living with metastatic pancreatic adenocarcinoma (mPDAC). This is the second approval for an Onivyde regimen in mPDAC, following the FDA's approval in 2015 of Onivyde plus fluorouracil and leucovorin following disease progression with gemcitabine-based therapy.

"The results from the Phase III NAPOLI 3 trial represent the first positive data for an investigational regimen in first-line metastatic pancreatic adenocarcinoma versus the currently approved nab-paclitaxel and gemcitabine regimen," said Christelle Huguet, EVP and Head of Research and Development, Ipsen. "With today's approval, this Onivyde (NALIRIFOX) regimen can now offer a potential new standard-of-care treatment option with proven survival benefits for people living with metastatic pancreatic adenocarcinoma in the U.S."

Pancreatic adenocarcinoma (PDAC) is the most common type of cancer that forms in the pancreas, with more than 60,000 people diagnosed in the U.S. each year and nearly 500,000 people globally.^{3,4} 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).⁵ Characterized as a complex cancer due to rapid tumor progression, limited genetic targets and multiple resistance mechanisms,⁶ mPDAC has a poor prognosis with fewer than 20% of people surviving longer than one year.^{4,5} Overall, pancreatic cancer has the lowest five-year survival rate of all cancer types globally and in the U.S.^{4,5}

"Metastatic pancreatic adenocarcinoma is a difficult disease to manage with very few available treatment options. Given the reality of this aggressive form of cancer and the complexity of the disease, every advance in the treatment landscape represents a meaningful improvement in patient outcomes," said Dr. Zev Wainberg, Professor of Medicine and Co-Director of the UCLA GI Oncology Program. "The approval of this Onivyde regimen is an important milestone for people living with mPDAC, their families and healthcare providers, with the NAPOLI 3 trial having demonstrated survival benefits versus a current standard of care treatment option."

"We are pleased that the U.S. Food and Drug Administration has issued this new approval of the NALIRIFOX regimen. With each new approved treatment, there is more hope for those who will be diagnosed in the future and people currently living with pancreatic cancer may have more time with their

loved ones,” said Julie Fleshman, JD, MBA, President and CEO of Pancreatic Cancer Action Network (PanCAN), a patient advocacy organization committed to providing evidence-based information and resources to patients and caregivers, along with advancing research to improve patient outcomes. “We are thankful to the patients who participated in this clinical trial as they play a crucial role in advancing treatments for pancreatic cancer.”

NAPOLI 3 data

The FDA approval was based on efficacy and safety data from NAPOLI 3, a randomized, open-label, Phase III pivotal trial that enrolled 770 people living with mPDAC between the ages of 20 and 85 without prior treatment across 187 trial site locations in 18 countries. The study, which met the primary and secondary endpoints, was presented as a late-breaking presentation at the ASCO Gastrointestinal conference 2023 and subsequently published in *The Lancet*.^{1,7} Additionally, NALIRIFOX was recognized by the National Comprehensive Cancer Network® (NCCN) guidelines* and recommended as a preferred, Category 1 treatment option in first-line metastatic disease and as a preferred option in first-line locally advanced disease.⁸

- The study demonstrated NALIRIFOX (n=383) provided a statistically significant improvement in median overall survival (mOS) of 11.1 months (95% confidence interval (CI) (10.0, 12.1)) compared to 9.2 months (95% CI (8.3, 10.6)) in nab-paclitaxel and gemcitabine treated patients (n=387); (hazard ratio (HR) 0.84 [95% CI 0.71–0.99]; p=0.0403).⁹
- NALIRIFOX regimen also demonstrated a statistically significant improvement in median progression-free survival (mPFS) of 7.4 months (95% CI (6.0, 7.7)) versus 5.6 months (95% CI (5.3, 5.8)) for nab-paclitaxel and gemcitabine treated patients (HR 0.70 [95% CI 0.59–0.85]; p=0.0001).⁹
- 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.⁹
- The safety profile of the Onivyde regimen was manageable and consistent with the profiles of the treatment components, with the potential of serious adverse events of fatal neutropenic fever and severe diarrhea. The most common Grade 3/4 treatment-emergent adverse events were diarrhea, fatigue, nausea, vomiting, decreased appetite, abdominal pain, mucosal inflammation, constipation and decreased weight.⁹ In NAPOLI 3, Grade 3 and 4 diarrhea (early and late-onset) occurred in 20% receiving NALIRIFOX. In the clinical trial, diarrhea was managed following institutional guidelines and appropriate antidiarrheal medications.⁹

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ENDS

About Onivyde (irinotecan liposome injection)

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 administered via intravenous infusion over 90 minutes every two weeks, with recommendations on dosing modifications. Onivyde may be prescribed immediately in the U.S. for eligible people living with mPDAC who are treatment naïve or following gemcitabine-based therapy.

To support access to Onivyde for eligible individuals in the U.S., Ipsen Cares patient support program is available as a resource to people living with mPDAC and their caregivers to provide educational support and address coverage, access and reimbursement questions (1-866-435-5677).

Onivyde is currently approved in most major markets including the U.S., Europe and Asia in combination with fluorouracil (FU) and leucovorin (LV) for the treatment of adult patients with metastatic pancreatic

adenocarcinoma after disease progression following gemcitabine-based therapy. Onivyde is not indicated as a single agent for the treatment of adult patients with metastatic pancreatic adenocarcinoma.

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.

Ipsen has exclusive commercialization rights for the current and potential future indications for Onivyde in the U.S. Servier, an independent international 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 more than 60,000 people diagnosed in the U.S. each year and nearly 500,000 people globally.^{3,4} 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).⁵ Weight loss, abdominal pain and jaundice are the most common symptoms, making PDAC difficult to detect.¹⁰ Despite significant advances in cancer treatments since the 1970s, no treatment options for PDAC significantly extend life.⁵ 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.^{3,4}

About the NAPOLI 3 trial¹

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 187 trial site locations in 18 countries across Europe, North America, South America, Asia, and Australia. Patients were randomized to receive Onivyde plus oxaliplatin, fluorouracil and leucovorin (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 Ipsen

We are a global biopharmaceutical company with a focus on bringing transformative medicines to patients in three therapeutic areas: Oncology, Rare Disease and Neuroscience.

Our pipeline is fueled by external innovation and supported by nearly 100 years of development experience and global hubs in the U.S., France and the U.K. Our teams in more than 40 countries and our partnerships around the world enable us to bring medicines to patients in more than 100 countries.

Ipsen 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 ipсен.com.

U.S. IMPORTANT SAFETY INFORMATION

Indications

- ONIVYDE® (irinotecan liposome injection) is indicated, in combination with oxaliplatin, fluorouracil, and leucovorin for the first-line treatment of adult patients with metastatic pancreatic adenocarcinoma.
- ONIVYDE is indicated, in combination with fluorouracil, and leucovorin, for the treatment of adult patients with metastatic pancreatic adenocarcinoma after disease progression following gemcitabine-based therapy.

Limitations of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic pancreatic adenocarcinoma.

WARNING: SEVERE Neutropenia and SEVERE DIARRHEA

Neutropenia

- **Severe and life-threatening neutropenia, including fatal neutropenic sepsis and fatal neutropenic fever, has occurred in patients receiving ONIVYDE in combination with oxaliplatin, fluorouracil and leucovorin and in combination with fluorouracil and leucovorin. Withhold ONIVYDE for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment.**

Diarrhea

- **Severe and life-threatening diarrhea has occurred in patients receiving ONIVYDE in combination with oxaliplatin, fluorouracil and leucovorin and in combination with fluorouracil and leucovorin. 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.**

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Severe Neutropenia: See Boxed WARNING. In NAPOLI 3, Grade 3 and 4 neutropenia occurred in 26% of patients receiving ONIVYDE in combination with oxaliplatin, fluorouracil, and leucovorin (NALIRIFOX) and fatal neutropenic fever in 0.3% of patients. In NAPOLI 3, the incidence of Grade 3 or 4 neutropenia was similar among Asian patients [6 of 20 (30%)] compared to White patients [76 of 289 (26%)]. Neutropenic fever/neutropenic sepsis was reported in 5% of Asian patients (1 of 20) compared to 2.3% of White patients (7 of 306). In NAPOLI-1, Grade 3 and 4 neutropenia occurred in 20% of patients receiving ONIVYDE in combination with fluorouracil and leucovorin (ONIVYDE/FU/LV). Neutropenic sepsis occurred in 3% and fatal neutropenic sepsis in 0.8%. In NAPOLI-1, the incidence of Grade 3 or 4 neutropenia was higher among Asian patients [18 of 33 (55%)] compared to White patients [13 of 73 (18%)]. Neutropenic fever/neutropenic sepsis was reported in 6% of Asian patients compared to 1% of White patients.

Severe Diarrhea: See Boxed WARNING. In NAPOLI 3, Grade 3 and 4 diarrhea (early-onset [within 24 hours of chemotherapy] and late-onset [more than 24 hours following chemotherapy]) occurred in 20% receiving NALIRIFOX. In NAPOLI-1, Grade 3 or 4 diarrhea occurred in 13% receiving ONIVYDE/FU/LV. The incidence of Grade 3 or 4 late-onset diarrhea was 9% in patients receiving ONIVYDE/FU/LV. The incidence of Grade 3 or 4 early-onset diarrhea was 3% in patients receiving ONIVYDE/FU/LV. To reduce the risk of severe diarrhea, patients should stop lactose-containing products, eat a low-fat diet, and maintain hydration during treatment with ONIVYDE. Withhold ONIVYDE for Grade 2-4 diarrhea. Local institutional guidelines should be followed for the treatment of diarrhea that does not improve within 48 hours and may include the addition of diphenoxylate hydrochloride plus atropine sulfate or octreotide. Following recovery to Grade 1 diarrhea, resume ONIVYDE at a reduced dose.

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 Reaction: Irinotecan, including ONIVYDE, 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 pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during and for 7 months after the last dose of ONIVYDE treatment.

ADVERSE REACTIONS FOR NALIRIFOX

- The most common adverse reactions ($\geq 20\%$ with a difference between arms of $\geq 5\%$ for all grades or $\geq 2\%$ for Grades 3 or 4 compared to nab-paclitaxel and gemcitabine) of NALIRIFOX were diarrhea (72%), fatigue (62%), nausea (59%), neutropenia (48%), vomiting (40%), decreased appetite (37%), abdominal pain (35%), hypokalemia (32%), mucosal inflammation (28%), constipation (25%) and weight decreased (22%).
- Permanent discontinuation of ONIVYDE due to an adverse reaction occurred in 17% of patients. Adverse reactions that resulted in permanent discontinuation of ONIVYDE in $\geq 1\%$ of patients included neutropenia, thrombocytopenia, diarrhea, fatigue, infections and cerebrovascular accident.
- Dosage reduction of ONIVYDE due to an adverse reaction occurred in 52% of patients. Adverse reactions that required dosage reduction in $\geq 1\%$ of patients included anemia, decreased appetite, diarrhea, fatigue, febrile neutropenia, hypokalemia, liver function test abnormalities, nausea, mucosal inflammation, neutropenia, peripheral neuropathy, vomiting, thrombocytopenia and weight decreased.
- Dosage interruptions of ONIVYDE due to an adverse reaction occurred in 1.9% of patients. Adverse reactions that required dosage interruption in $\geq 0.5\%$ of patients included hypersensitivity and infusion related reaction.
- The most common laboratory abnormalities ($\geq 10\%$ Grade 3 or 4) were decreased neutrophils (26%), decreased potassium (22%), decreased lymphocytes (11%) and decreased hemoglobin (10%).

ADVERSE REACTIONS FOR ONIVYDE/5-FU/LV

- The most common adverse reactions ($\geq 20\%$) were diarrhea (59%), fatigue/asthenia (56%), vomiting (52%), nausea (51%), decreased appetite (44%), stomatitis (32%), and pyrexia (23%).
- 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 ($\geq 10\%$ Grade 3 or 4) were lymphopenia and neutropenia.

Postmarketing Experience: Immune system disorders: Hypersensitivity (including anaphylactic reaction and angioedema)

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

To report SUSPECTED ADVERSE REACTIONS, contact Ipsen Biopharmaceuticals, Inc. at 1-855-463-5127 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full [Prescribing Information](#), including Boxed WARNING for ONIVYDE.

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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

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References

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- ⁴ <https://www.cancer.net/cancer-types/pancreatic-cancer/statistics>
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- ⁸ <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1455>
- ⁹ FDA U.S. Prescribing Information. https://d2rkmuse97gwnh.cloudfront.net/a88aa6d6-3ca0-4362-a711-d53c45ae33ff/68b50c8f-8577-4904-950d-d82fa1f91417/68b50c8f-8577-4904-950d-d82fa1f91417_source_v.pdf
- ¹⁰ www.cancer.org/cancer/types/pancreatic-cancer/detection-diagnosis-staging/signs-and-symptoms