



# DOSING GUIDE

## 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

### **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 5-FU and LV. Withhold ONIVYDE for absolute neutrophil count below  $1500/\text{mm}^3$  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.

Please see additional [Important Safety Information](#) throughout and accompanying [Full Prescribing Information](#), including Boxed Warning, for ONIVYDE®.

# ABOUT THIS GUIDE

This dosing guide contains key product information about ONIVYDE® (irinotecan liposome injection), the recommended dosing regimen, as well as appropriate dose modifications that can be used to manage adverse reactions.



\*Does not represent actual packaging.

Please see additional [Important Safety Information](#) throughout and accompanying [Full Prescribing Information](#), including Boxed Warning, for ONIVYDE®.

# PRODUCT INFORMATION<sup>1</sup>

## DOSAGE FORM AND STRENGTH

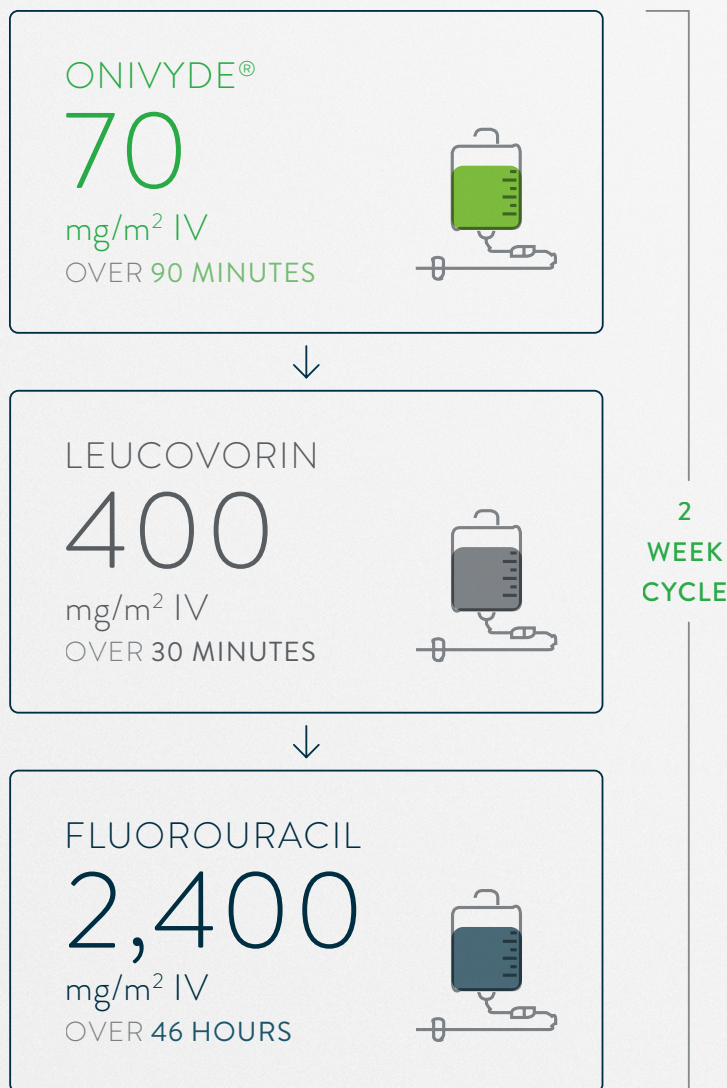
- ONIVYDE® is a sterile, white to slightly yellow opaque isotonic liposomal dispersion
  - Each 10 mL single-dose vial contains 43 mg irinotecan free base at a concentration of 4.3 mg/mL

## STORAGE AND HANDLING

- Refrigerate ONIVYDE® 10 mL vial at 2°C to 8°C (36°F to 46°F)
- Do NOT freeze
- Protect from light
- Storage following dilution:
  - Administer diluted solution within 4 hours of preparation when stored at room temperature or within 24 hours of preparation when stored under refrigerated conditions
  - Protect diluted solution from light
- Discard any unused portion



# RECOMMENDED DOSING PROTOCOL<sup>1</sup>



Administer ONIVYDE® (irinotecan liposome injection) 70 mg/m<sup>2</sup> intravenously over 90 minutes, prior to leucovorin and fluorouracil, every 2 weeks.\*

Please see additional [Important Safety Information](#) throughout and accompanying [Full Prescribing Information](#), including Boxed Warning, for ONIVYDE®.

## PREMEDICATION<sup>1</sup>

Premedicate with a corticosteroid and an anti-emetic 30 minutes prior to ONIVYDE® infusion.

## STARTING DOSE CONSIDERATIONS<sup>1</sup>

The recommended starting dose of ONIVYDE® in patients known to be homozygous for the UGT1A1\*28 allele is **50 mg/m<sup>2</sup>** administered by IV infusion over 90 minutes.

- Increase the dose of ONIVYDE® to 70 mg/m<sup>2</sup>, as tolerated, in subsequent cycles

There is no recommended dose of ONIVYDE® for patients with serum bilirubin above the upper limit of normal.

## IN THE NAPOLI-1<sup>†</sup> TRIAL<sup>1,2</sup>:

- Treatment continued until disease progression or unacceptable toxicity
- The median duration of therapy in the ONIVYDE® + 5-FU/LV arm was 9 weeks

## SELECTED IMPORTANT SAFETY INFORMATION

### 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.

\*Please see leucovorin and fluorouracil Prescribing Information for administration, storage, and handling information.

<sup>†</sup>NAPOLI-1 was a global, phase 3, randomized, open-label, multicenter trial in patients (N=417) with metastatic adenocarcinoma of the pancreas whose disease had progressed following gemcitabine-based therapy. Patients were initially randomized to receive ONIVYDE® (100 mg/m<sup>2</sup> every three weeks) or 5-FU/LV. After 63 patients were enrolled, a third arm, ONIVYDE® (70 mg/m<sup>2</sup> every two weeks) + 5-FU/LV, was added. Treatment was continued until disease progression or unacceptable toxicity. The primary endpoint was median OS. Additional efficacy endpoints were PFS (progression-free survival) and ORR (objective response rate).<sup>1,3</sup>

5-FU=fluorouracil; LV=leucovorin; OS=overall survival.





# ADDITIONAL CONSIDERATIONS<sup>1</sup>

## IMPORTANT USE INFORMATION

- Do not substitute ONIVYDE® for other drugs containing irinotecan hydrochloride
- Monitor complete blood cell counts on Days 1 and 8 of every cycle and more frequently if clinically indicated
- Avoid the use of strong CYP3A4 inducers if possible; substitute non-enzyme-inducing therapies at least 2 weeks prior to initiation of ONIVYDE®
- Avoid the use of strong CYP3A4 or UGT1A1 inhibitors, if possible; discontinue strong CYP3A4 inhibitors at least 1 week prior to starting therapy

## PREPARATION AND ADMINISTRATION

- ONIVYDE® is a cytotoxic drug. Follow applicable special handling and disposal procedures
- Calculate the exact total dosing volume of 4.3 mg/mL ONIVYDE® solution required for the patient and slowly withdraw from the vial into a syringe
  - Dilute ONIVYDE® in 500 mL D5W (dextrose 5% water) or NS (normal saline 0.9%)
  - Mix diluted solution by gently inverting (do not shake)
- Allow diluted solution to reach room temperature prior to administration
- Infuse diluted solution intravenously over 90 minutes
  - Do not use in-line filters

Please see additional [Important Safety Information](#) throughout and accompanying [Full Prescribing Information](#), including Boxed Warning, for ONIVYDE®.



# RECOMMENDED DOSE MODIFICATIONS<sup>1</sup>

## ONIVYDE® + 5-FU/LV OFFERS A PROTOCOL FOR DOSE REDUCTION, DELAY, AND DISCONTINUATION

Toxicity NCI CTCAE v4.0*	Directions	ONIVYDE® adjustment in patients receiving 70 mg/m <sup>2</sup>	Patients homozygous for UGT1A1*28 (who are currently receiving 50 mg/m <sup>2</sup> )
Grade 2 Diarrhea	Withhold ONIVYDE®. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity	N/A	N/A
Grade 3 or 4 Diarrhea	Withhold ONIVYDE®. Initiate loperamide for late- onset diarrhea of any severity. Administer intravenous or subcutaneous atropine 0.25 to 1 mg (unless clinically contraindicated) for early onset diarrhea of any severity. Upon recovery to ≤Grade 1, resume ONIVYDE® at a modified dose	<b>FIRST OCCURRENCE</b> 50 mg/m <sup>2</sup> 43 mg/m <sup>2</sup>	
		<b>SECOND OCCURRENCE</b> 43 mg/m <sup>2</sup> 35 mg/m <sup>2</sup>	
		<b>THIRD OCCURRENCE</b> Discontinue ONIVYDE®	
Grade 3 or 4 Adverse Reactions	Withhold ONIVYDE®. Upon recovery to ≤Grade 1, resume ONIVYDE® at a modified dose	<b>FIRST OCCURRENCE</b> 50 mg/m <sup>2</sup> 43 mg/m <sup>2</sup>	
		<b>SECOND OCCURRENCE</b> 43 mg/m <sup>2</sup> 35 mg/m <sup>2</sup>	
		<b>THIRD OCCURRENCE</b> Discontinue ONIVYDE®	
Interstitial Lung Disease	<b>FIRST OCCURRENCE</b> Discontinue ONIVYDE®		
Anaphylactic Reaction	<b>FIRST OCCURRENCE</b> Discontinue ONIVYDE®		

\*National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 used for grading.

For recommended dose modifications and toxicities of 5-FU/LV, refer to the Full Prescribing Information.

Please see additional [Important Safety Information](#) throughout and accompanying [Full Prescribing Information](#), including Boxed Warning, for ONIVYDE®.

## IN THE NAPOLI-1 TRIAL:

- When ONIVYDE® was withheld or discontinued for adverse reactions, 5-FU was also withheld or discontinued
- When the dose of ONIVYDE® was reduced for adverse reactions, the dose of 5-FU was reduced by 25%

## DOSE REDUCTIONS

- 33% of patients dose reduced ONIVYDE® + 5-FU/LV
  - Adverse reactions leading to dose reductions of ONIVYDE® were neutropenia, diarrhea, nausea, and anemia

## DELAYS

- 62% of patients withheld or delayed ONIVYDE® + 5-FU/LV
  - Adverse reactions leading to withholding or delaying ONIVYDE® were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia

## DISCONTINUATIONS

- 11% of patients discontinued ONIVYDE® + 5-FU/LV
  - Adverse reactions leading to permanent discontinuation of ONIVYDE® included diarrhea, vomiting, and sepsis

## MEDIAN DURATION OF THERAPY

- In NAPOLI-1 the median duration of therapy in the ONIVYDE® + 5-FU/LV arm was 9 weeks





# RECOMMENDED DOSE MODIFICATIONS<sup>1</sup> (CONT'D)



## MANAGEMENT OF SEVERE NEUTROPENIA

- Monitor complete blood cell counts on Days 1 and 8 of every cycle and more frequently if clinically indicated
- Withhold ONIVYDE® for absolute neutrophil count below 1500/mm<sup>3</sup> or neutropenic fever
- Upon recovery to ANC  $\geq 1500/\text{mm}^3$ , reduce ONIVYDE® dose for Grade 3–4 neutropenia or neutropenic fever
- Special Considerations:
  - 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



## MANAGEMENT OF SEVERE DIARRHEA

- Severe or life-threatening diarrhea followed one of two patterns:
  - Late-onset diarrhea (onset more than 24 hours following chemotherapy); and
  - Early-onset diarrhea (onset within 24 hours of chemotherapy, sometimes occurring with other symptoms of cholinergic reaction)
- An individual patient may experience both early- and late-onset diarrhea
- Withhold ONIVYDE® for diarrhea of Grade 2–4 severity
- Administer loperamide for late diarrhea of any severity; 34% of patients received loperamide for late-onset diarrhea
- Administer atropine for early diarrhea of any severity; 26% of patients received atropine for early-onset diarrhea
- Following recovery to Grade 1 diarrhea, resume ONIVYDE® at a reduced dose

Please see additional [Important Safety Information](#) throughout and accompanying [Full Prescribing Information](#), including Boxed Warning, for ONIVYDE®.



# IMPORTANT SAFETY INFORMATION

## 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.

### **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 5-FU and LV. Withhold ONIVYDE for absolute neutrophil count below 1500/mm<sup>3</sup> 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 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.

## WARNINGS AND PRECAUTIONS (CONT'D)

### **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 ≤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.





# IMPORTANT SAFETY INFORMATION (CONT'D)

## 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.

## ADVERSE REACTIONS (CONT'D)

- 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  $\geq 2$  weeks prior to initiation of ONIVYDE. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors, if possible, and discontinue strong CYP3A4 inhibitors  $\geq 1$  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/m<sup>2</sup> 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/m<sup>2</sup> 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 additional [Important Safety Information](#) throughout and accompanying [Full Prescribing Information](#), including Boxed Warning, for ONIVYDE®.

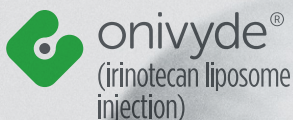




THE EVIDENCE TO

# FIGHT ON

with ONIVYDE® + 5-FU/LV



FDA-approved therapy in post-gemcitabine metastatic pancreatic cancer, in combination with 5-FU/LV<sup>1</sup>



Only Category 1 National Comprehensive Cancer Network® (NCCN®) chemotherapy recommended & FDA-approved in post-gemcitabine metastatic pancreatic cancer<sup>4\*†</sup>



Safety profile studied in a large phase 3 trial<sup>1,3</sup>

## SELECTED IMPORTANT SAFETY INFORMATION

### ADVERSE REACTIONS

- The most common (≥20%) adverse reactions in which patients receiving ONIVYDE + 5-FU/LV experienced a ≥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%).

\* Liposomal irinotecan + 5-FU/LV is the only Category 1 NCCN chemotherapy recommendation for patients with post-gemcitabine metastatic pancreatic cancer with good performance status and disease progression.

† NCCN® makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Please see additional [Important Safety Information](#) throughout and accompanying [Full Prescribing Information](#), including **Boxed Warning**, for ONIVYDE®.

**References:** 1. ONIVYDE® [package insert]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc.; 2017. 2. Data on file #1. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc.; 2015. 3. Wang-Gillam A, Li C-P, Bodoky G, et al. *Lancet*. 2016;387:545-557. 4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pancreatic Adenocarcinoma V.3.2017. ©National Comprehensive Cancer Network, Inc. 2017. All rights reserved. Accessed November 2, 2017. To view the most recent and complete version of the guideline, go online to [NCCN.org](http://NCCN.org). NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

**FOR MORE INFORMATION, PLEASE VISIT [ONIVYDE.COM](http://ONIVYDE.COM)**



©2020 Ipsen Biopharmaceuticals, Inc. All rights reserved.  
ONIVYDE is a registered trademark of Ipsen Biopharm Ltd.  
All other trademarks are the property of their respective owners.  
August 2020 ONV-US-002723