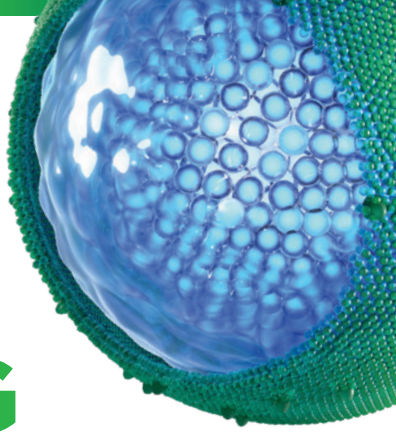
onivyde®
(irinotecan liposome injection)



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/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 on pages 12-15 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 help manage adverse reactions.

*Does not represent actual packaging.

For intravenous infusion after dilution. Do not substitute for irinotecan hydrochloride.

PRODUCT INFORMATION[1]

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

Please see additional Important Safety Information on pages 12-15 and accompanying full Prescribing Information, including Boxed WARNING, for ONIVYDE.

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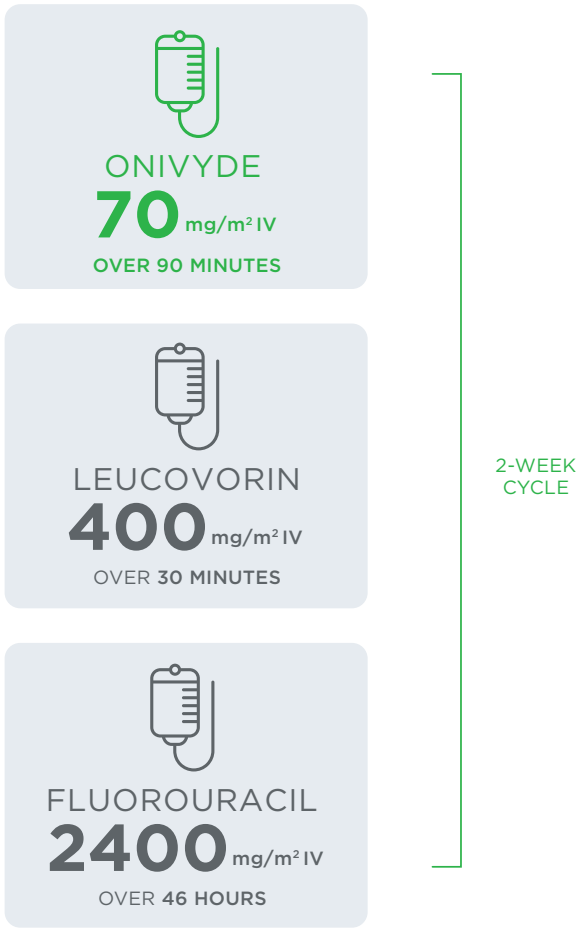
RECOMMENDED DOSING PROTOCOL[1]



Colors are for illustrative purposes only.

Administer ONIVYDE® (irinotecan liposome injection) 70 mg/m² intravenously over 90 minutes, prior to leucovorin and fluorouracil, every 2 weeks.*

IMPORTANT SAFETY INFORMATION (CONT'D)

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

Premedication[1]

Premedicate with a corticosteroid and an antiemetic 30 minutes prior to ONIVYDE infusion.

Starting dose considerations[1]

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.

Increase the dose of ONIVYDE to 70 mg/m², 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† trial[1,2]

Treatment continued until disease progression or unacceptable toxicity

The median duration of therapy in the ONIVYDE + 5-FU/LV arm was 9 weeks

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

†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/m² every three weeks) or 5-FU/LV. After 63 patients were enrolled, a third arm, ONIVYDE® (70 mg/m² 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).[1,2]

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

Please see additional Important Safety Information on pages 12-15 and accompanying full Prescribing Information, including Boxed WARNING, for ONIVYDE.

onivyde® (irinotecan liposome injection)

ADDITIONAL CONSIDERATIONS[1]

When metastatic pancreatic ductal adenocarcinoma (mPDAC) progresses on gemcitabine

Actor portrayal

Consider ONIVYDE® (irinotecan liposome injection) + 5-FU/LV—the #1 prescribed and only FDA-approved regimen for mPDAC post-gemcitabine[1,3*]

*Based on metastatic pancreatic cancer patients who have had at least 3 cycles of a gemcitabine-based regimen and did not have pancreatic cancer-related activity for 60 days prior to beginning an ONIVYDE treatment regimen. Based on data from Q4 2016 through Q3 2021.[3]

IMPORTANT SAFETY INFORMATION (CONT'D)

CONTRAINDICATION

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

Please see additional Important Safety Information on pages 12-15 and accompanying full Prescribing Information, including Boxed WARNING, for ONIVYDE.

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

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RECOMMENDED DOSE MODIFICATIONS[1]

ONIVYDE® (irinotecan liposome injection) + 5-FU/LV offers a protocol for dose reduction, delay, and discontinuation

Toxicity NCI CTCAE v4.0*	ONIVYDE adjustment in patients receiving 70 mg/m²	Patients homozygous for UGT1A1*28 (who are currently receiving 50 mg/m²)
Grade 2 Diarrhea DIRECTIONS: Withhold ONIVYDE. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity.	N/A	
Grade 3 or 4 Diarrhea DIRECTIONS: 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.	FIRST OCCURRENCE 50 mg/m² 43 mg/m² SECOND OCCURRENCE 43 mg/m² 35 mg/m²	
Grade 3 or 4 Adverse Reactions DIRECTIONS: Withhold ONIVYDE. Upon recovery to ≤Grade 1, resume ONIVYDE at a modified dose.	THIRD OCCURRENCE Discontinue ONIVYDE	
Interstitial Lung Disease	FIRST OCCURRENCE Discontinue ONIVYDE	
Anaphylactic Reaction	FIRST OCCURRENCE Discontinue ONIVYDE	

*National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) 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 on pages 12-15 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%

Delays

- 62% of patients withheld or delayed ONIVYDE + 5-FU/LV, most frequently due to neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia

Dose reductions

- 33% of patients dose reduced ONIVYDE + 5-FU/LV, most frequently due to neutropenia, diarrhea, nausea, and anemia

Discontinuations

- 11% of patients discontinued ONIVYDE + 5-FU/LV, most frequently due to 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

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RECOMMENDED DOSE MODIFICATIONS[1] (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® (irinotecan liposome injection) for absolute neutrophil count (ANC) below 1500/mm^3 or neutropenic fever
- Resume ONIVYDE when the ANC is 1500/mm^3 or above
- Reduce ONIVYDE dose for Grade 3-4 neutropenia or neutropenic fever following recovery in subsequent cycles
- Special considerations:
  - 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

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 on pages 12-15 and accompanying full Prescribing Information, including Boxed WARNING, for ONIVYDE.

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INDICATION AND 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^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**

CONTRAINDICATION

- 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 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 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 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 females of reproductive potential to use effective contraception during and for 7 months after the last dose of 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%)

Please see additional Important Safety Information on pages 14-15 and accompanying full Prescribing Information, including Boxed WARNING, for ONIVYDE.

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INDICATION AND IMPORTANT SAFETY INFORMATION (CONT'D)

ADVERSE REACTIONS (CONT'D)

- 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%)
- The following adverse reactions have been identified during post approval use of ONIVYDE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

  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.

DOSAGE AND ADMINISTRATION

The recommended dose of ONIVYDE is 70 mg/m^2 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^2 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 antiemetic 30 minutes prior to ONIVYDE. Withhold ONIVYDE for Grade 3/4 adverse reactions. Resume ONIVYDE with reduced dose once adverse reaction recovered to ≤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 on pages 12-14 and accompanying full Prescribing Information, including Boxed WARNING, for ONIVYDE.

References: 1. ONIVYDE® [package insert]. Basking Ridge, NJ. Ipsen Biopharmaceuticals, Inc; 2023. **2.** Wang-Gillam A, Li C-P, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet*. 2016;387(10018):545-557. **3.** Ipsen data on file: IQVIA medical claims post-gemcitabine usage analysis, June 2018 – October 2021. **4.** Zhang H. Onivyde for the therapy of multiple solid tumors. *Onco Targets Ther*. 2016;9:3001-3007. **5.** Dimou A, Syrigos KN, Saif MW. Overcoming the stromal barrier: technologies to optimize drug delivery in pancreatic cancer. *Ther Adv Med Oncol*. 2012;4(5):271-279. **6.** Drummond DC, Noble CO, Guo Z, Hong K, Park JW, Kirpotin DB. Development of a highly active nanoliposomal irinotecan using a novel intraliposomal stabilization strategy. *Cancer Res*. 2006;66(6):3271-3277. **7.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pancreatic Adenocarcinoma V.1.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed May 5, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org.

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Proven to EXTEND OVERALL SURVIVAL[1]

- ONIVYDE® (irinotecan liposome injection) + 5-FU/LV increased median OS by approximately 2 months vs 5-FU/LV alone (6.1 vs 4.2 months)
- The most common serious adverse reactions (≥2%) of ONIVYDE were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia

Designed for PROLONGED CIRCULATION[1,4-6]

- Prolonged circulation time allows ONIVYDE to deliver its cytotoxic payload to the tumor

Category 1 RECOMMENDED OPTION[7*]

- Liposomal irinotecan (ONIVYDE) + 5-FU/LV is a Category 1 NCCN recommended option for mPDAC following gemcitabine-based therapy

Scan the QR code to learn more about ONIVYDE

IMPORTANT SAFETY INFORMATION (CONT'D)
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%)

*National Comprehensive Cancer Network® (NCCN®) Category 1 Recommendation: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[7] 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.

For more information, please visit **www.ONIVYDE.com**

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