

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of the information needed to use ONIVYDE® safely and effectively. See full prescribing information for ONIVYDE®.

ONIVYDE® (irinotecan liposome injection), for intravenous use
Initial U.S. Approval: 1996

WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA

See full prescribing information for complete boxed warning

- 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 and leucovorin. Withhold ONIVYDE for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment (2.2), (5.1).
- Severe diarrhea occurred in 13% of patients receiving ONIVYDE 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 (2.2), (5.2).

RECENT MAJOR CHANGES

Contraindications (4)	02/2023
Warnings and Precautions (5.4, 5.5)	02/2023

INDICATIONS AND USAGE

ONIVYDE is a topoisomerase inhibitor indicated, in combination with fluorouracil and leucovorin, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy. (1)

Limitation of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas. (1)

DOSAGE AND ADMINISTRATION

- Do not substitute ONIVYDE for other drugs containing irinotecan HCl. (2.1)
- Recommended dose of ONIVYDE is 70 mg/m² intravenous infusion over 90 minutes every two weeks. (2.2)
- Recommended starting dose of ONIVYDE in patients homozygous for UGT1A1*28 is 50 mg/m² every two weeks. (2.2)

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- There is no recommended dose of ONIVYDE for patients with serum bilirubin above the upper limit of normal. (2.2)
- Premedicate with a corticosteroid and an anti-emetic. 30 minutes prior to ONIVYDE. (2.2)

DOSAGE FORMS AND STRENGTHS

Injection: 43 mg/10 mL single dose vial (3)

CONTRAINDICATIONS

Severe hypersensitivity reaction to ONIVYDE or irinotecan HCl. (4, 5.4)

WARNINGS AND PRECAUTIONS

- Interstitial lung disease (ILD): Fatal ILD has occurred in patients receiving irinotecan HCl. Discontinue ONIVYDE if ILD is diagnosed. (5.3)
- Severe hypersensitivity reaction: Permanently discontinue ONIVYDE for severe hypersensitivity reactions. (5.4, 4)
- Embryo-fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.5, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (≥ 20%) of ONIVYDE: diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common laboratory abnormalities (≥ 10% Grade 3 or 4) were lymphopenia and neutropenia. (6)

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.

DRUG INTERACTIONS

- Strong CYP3A4 Inducers: Avoid the use of strong CYP3A4 inducers if possible. Substitute non-enzyme inducing therapies at least 2 weeks prior to initiation of ONIVYDE. (7.1)
- Strong CYP3A4 Inhibitors: Avoid the use of strong CYP3A4 or UGT1A1 inhibitors, if possible; discontinue strong CYP3A4 inhibitors at least 1 week prior to starting therapy. (7.2)

USE IN SPECIFIC POPULATIONS

- Lactation: Do not breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 02/2023

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FULL PRESCRIBING 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 fluorouracil and leucovorin. Withhold ONIVYDE for absolute neutrophil count below 1500/mm³ or neutropenic fever. Monitor blood cell counts periodically during treatment [see *Dosage and Administration (2.2)* and *Warnings and Precautions (5.1)*].

Severe diarrhea occurred in 13% of patients receiving ONIVYDE 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 [see *Dosage and Administration (2.2)* and *Warnings and Precautions (5.2)*].

1 INDICATIONS AND USAGE

ONIVYDE® is indicated, in combination with fluorouracil and leucovorin, 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 [see *Clinical Studies (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 Important Use Information

DO NOT SUBSTITUTE ONIVYDE for other drugs containing irinotecan HCl.

2.2 Recommended Dose

Administer ONIVYDE prior to leucovorin and fluorouracil [see *Clinical Studies (14)*].

- The recommended dose of ONIVYDE is 70 mg/m² administered by intravenous infusion over 90 minutes every 2 weeks.
- The recommended starting dose of ONIVYDE in patients known to be homozygous for the UGT1A1*28 allele is 50 mg/m² administered by intravenous 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 [see *Adverse Reactions (6.1)* and *Clinical Studies (14)*].

Premedication

Administer a corticosteroid and an anti-emetic 30 minutes prior to ONIVYDE infusion.

2.3 Dose Modifications for Adverse Reactions

Table 1: Recommended Dose Modifications for ONIVYDE

Toxicity NCI CTCAE v4.0 [†]	Occurrence	ONIVYDE adjustment in patients receiving 70 mg/m ²	Patients homozygous for UGT1A1*28 without previous increase to 70 mg/m ²
Grade 3 or 4 adverse reactions	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:		
	First	50 mg/m ²	43 mg/m ²
	Second	43 mg/m ²	35 mg/m ²
	Third	Discontinue ONIVYDE	Discontinue ONIVYDE
Interstitial Lung Disease	First	Discontinue ONIVYDE	Discontinue ONIVYDE
Anaphylactic Reaction	First	Discontinue ONIVYDE	Discontinue ONIVYDE

[†] NCI CTCAE v 4.0=National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0

For recommended dose modifications of fluorouracil (5-FU) or leucovorin (LV), refer to the Full Prescribing Information; refer to Clinical Studies (14).

2.4 Preparation and Administration

ONIVYDE is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹

Preparation

- Withdraw the calculated volume of ONIVYDE from the vial. Dilute ONIVYDE in 500 mL 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP and mix diluted solution by gentle inversion.
- Protect diluted solution from light.
- Administer diluted solution within 4 hours of preparation when stored at room temperature or within 24 hours of preparation when stored under refrigerated conditions [2°C to 8°C (36°F to 46°F)]. Allow diluted solution to come to room temperature prior to administration.
- Do NOT freeze.

Administration

- Infuse diluted solution intravenously over 90 minutes. Do not use in-line filters. Discard unused portion.

3 DOSAGE FORMS AND STRENGTHS

Injection: 43 mg/10 mL irinotecan free base as a white to slightly yellow, opaque, liposomal dispersion in a single-dose vial.

4 CONTRAINDICATIONS

ONIVYDE is contraindicated in patients who have experienced a severe hypersensitivity reaction or anaphylaxis to ONIVYDE or irinotecan HCl. [see *Warnings and Precautions (5.4), Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Severe Neutropenia

ONIVYDE can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In Study 1, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE, occurring in one of 117 patients in the ONIVYDE plus fluorouracil/leucovorin (ONIVYDE/5-FU/LV) arm and one of 147 patients receiving ONIVYDE as a single agent. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE/5-FU/LV compared to 2% of patients receiving fluorouracil/leucovorin alone (5-FU/LV). Grade 3 or 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 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 [see *Clinical Pharmacology (12.3)*].

Monitor complete blood cell counts on Days 1 and 8 of every cycle and more frequently if clinically indicated. Withhold ONIVYDE if the absolute neutrophil count (ANC) is below 1500/mm³ or if neutropenic fever occurs. Resume ONIVYDE when the ANC is 1500/mm³ or above. Reduce ONIVYDE dose for Grade 3-4 neutropenia or neutropenic fever following recovery in subsequent cycles [see *Dosage and Administration (2.2)*].

5.2 Severe Diarrhea

ONIVYDE can cause severe and life-threatening diarrhea. Do not administer ONIVYDE to patients with bowel obstruction.

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) [see *Cholinergic Reactions (6.1)*]. An individual patient may experience both early and late-onset diarrhea.

In Study 1, Grade 3 or 4 diarrhea occurred in 13% receiving ONIVYDE/5-FU/LV compared to 4% receiving 5-FU/LV. The incidence of Grade 3 or 4 late onset diarrhea was 9% in patients receiving ONIVYDE/5-FU/LV, compared to 4% in patients receiving 5-FU/LV. The incidence of Grade 3 or 4 early onset diarrhea was 3% in patients receiving ONIVYDE/5-FU/LV, compared to no Grade 3 or 4 early onset diarrhea in patients receiving 5-FU/LV. Of patients receiving ONIVYDE/5-FU/LV in Study 1, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea. Withhold ONIVYDE for Grade 2-4 diarrhea. 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. Following recovery to Grade 1 diarrhea, resume ONIVYDE at a reduced dose [see *Dosage and Administration (2.2)*].

5.3 Interstitial Lung Disease

Irinotecan HCl can cause severe and fatal interstitial lung disease (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.

5.4 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. [see *Contraindications (4), Adverse reactions (6.2)*]

5.5 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. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE 70 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE and for seven months following the last dose [see *Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)*].

6 ADVERSE REACTIONS

The following adverse drug reactions are discussed in greater detail in other sections of the label:

- Severe Neutropenia [see *Warnings and Precautions (5.1) and Boxed Warning*]
- Severe Diarrhea [see *Warnings and Precautions (5.2) and Boxed Warning*]

- Interstitial Lung Disease [see *Warnings and Precautions (5.3)*]
- Severe Hypersensitivity Reactions [see *Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of ONIVYDE cannot be directly compared to rates in clinical trials of other drugs and may not reflect the rates observed in practice.

The safety data described below are derived from patients with metastatic adenocarcinoma of the pancreas previously treated with gemcitabine-based therapy who received any part of protocol-specified therapy in Study 1, an international, randomized, active-controlled, open-label trial. Protocol-specified therapy consisted of ONIVYDE 70 mg/m² with leucovorin 400 mg/m² and fluorouracil 2400 mg/m² over 46 hours every 2 weeks (ONIVYDE/5-FU/LV; N=117), ONIVYDE 100 mg/m² every 3 weeks (N=147), or leucovorin 200 mg/m² and fluorouracil 2000 mg/m² over 24 hours weekly for 4 weeks followed by 2 week rest (5-FU/LV; N=134) [see *Clinical Studies (14)*]. Serum bilirubin within the institutional normal range, albumin \geq 3 g/dL, and Karnofsky Performance Status (KPS) \geq 70 were required for study entry. The median duration of exposure was 9 weeks in the ONIVYDE/5-FU/LV arm, 9 weeks in the ONIVYDE monotherapy arm, and 6 weeks in the 5-FU/LV arm.

The most common adverse reactions (\geq 20%) of ONIVYDE were diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common, severe laboratory abnormalities (\geq 10% Grade 3 or 4) were lymphopenia and neutropenia. 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.

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.

[Table 2](#) provides the frequency and severity of adverse reactions in Study 1 that occurred with higher incidence (\geq 5% difference for Grades 1-4 or \geq 2% difference for Grades 3-4) in patients who received ONIVYDE/5-FU/LV compared to patients who received 5-FU/LV.

Table 2: Adverse Reactions with Higher Incidence ($\geq 5\%$ Difference for Grades 1-4* or $\geq 2\%$ Difference for Grades 3 and 4) in the ONIVYDE/5-FU/LV Arm

Adverse Reaction	ONIVYDE/5-FU/LV N=117		5-FU/LV N=134	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal disorders				
Diarrhea	59	13	26	4
Early diarrhea [†]	30	3	15	0
Late diarrhea [‡]	43	9	17	4
Vomiting	52	11	26	3
Nausea	51	8	34	4
Stomatitis [§]	32	4	12	1
Infections and infestations				
Sepsis	4	3	2	1
Neutropenic fever/neutropenic sepsis [*]	3	3	1	0
Gastroenteritis	3	3	0	0
Intravenous catheter-related infection	3	3	0	0
General disorders and administration site conditions				
Fatigue/asthenia	56	21	43	10
Pyrexia	23	2	11	1
Metabolism and nutrition disorders				
Decreased appetite	44	4	32	2
Weight loss	17	2	7	0
Dehydration	8	4	7	2
Skin and subcutaneous tissue disorders				
Alopecia	14	1	5	0

* NCI CTCAE v4.0

[†] Early diarrhea: onset within 24 hours of ONIVYDE administration

[‡] Late diarrhea: onset >1 day after ONIVYDE administration

[§] Includes stomatitis, aphthous stomatitis, mouth ulceration, mucosal inflammation.

^{*} Includes febrile neutropenia

Cholinergic Reactions: 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. In Study 1, Grade 1 or 2 cholinergic symptoms other than early diarrhea occurred in 12 (4.5%) ONIVYDE-treated patients. Six of these 12 patients received atropine and in 1 of the 6 patients, atropine was administered for cholinergic symptoms other than diarrhea.

Infusion Reactions: 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.

Laboratory abnormalities that occurred with higher incidence in the ONIVYDE/5-FU/LV arm compared to the 5-FU/LV arm ($\geq 5\%$ difference) are summarized in the following table.

Table 3: Laboratory Abnormalities with Higher Incidence (≥5% Difference) in the ONIVYDE/5-FU/LV Arm^{*#}

Laboratory abnormality	ONIVYDE/5-FU/LV N=117		5-FU/LV N=134	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	97	6	86	5
Lymphopenia	81	27	75	17
Neutropenia	52	20	6	2
Thrombocytopenia	41	2	33	0
Hepatic				
Increased alanine aminotransferase (ALT)	51	6	37	1
Hypoalbuminemia	43	2	30	0
Metabolic				
Hypomagnesemia	35	0	21	0
Hypokalemia	32	2	19	2
Hypocalcemia	32	1	20	0
Hypophosphatemia	29	4	18	1
Hyponatremia	27	5	12	3
Renal				
Increased creatinine	18	0	13	0

* NCI CTCAE v4.0, worst grade shown.

Percent based on number of patients with a baseline and at least one post-baseline measurement.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval 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)

7 DRUG INTERACTIONS

7.1 Strong CYP3A4 Inducers

Following administration of non-liposomal irinotecan (i.e., irinotecan HCl), exposure to irinotecan or its active metabolite, SN-38, is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin and strong CYP3A4 inducers. Avoid the use of strong CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, St. John's wort) if possible. Substitute non-enzyme inducing therapies at least 2 weeks prior to initiation of ONIVYDE therapy [see *Clinical Pharmacology (12.3)*].

7.2 Strong CYP3A4 or UGT1A1 Inhibitors

Following administration of non-liposomal irinotecan (i.e., irinotecan HCl), patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to

irinotecan and its active metabolite SN-38. Co-administration of ONIVYDE with other inhibitors of CYP3A4 (e.g., clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 (e.g., atazanavir, gemfibrozil, indinavir) may increase systemic exposure to irinotecan or SN-38. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors if possible. Discontinue strong CYP3A4 inhibitors at least 1 week prior to starting ONIVYDE therapy [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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 [see *Clinical Pharmacology (12.1)*]. There are no available data in pregnant women. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE 70 mg/m² in humans, administered to pregnant rats and rabbits during organogenesis [see *Data*]. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

No animal studies have been conducted to evaluate the effect of irinotecan liposome on reproduction and fetal development; however, studies have been conducted with irinotecan HCl. Irinotecan crosses the placenta of rats following intravenous administration. Intravenous administration of irinotecan at a dose of 6 mg/kg/day to rats and rabbits during the period of organogenesis resulted in increased post-implantation loss and decreased numbers of live fetuses. In separate studies in rats, this dose resulted in an irinotecan exposure of approximately 0.002 times the exposure of irinotecan based on area under the curve (AUC) in patients administered ONIVYDE at the 70 mg/m² dose. Administration of irinotecan HCl resulted in structural abnormalities and growth delays in rats at doses greater than 1.2 mg/kg/day (approximately 0.0002 times the clinical exposure to irinotecan in ONIVYDE based on AUC). Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan HCl administered to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring.

8.2 Lactation

Risk Summary

There is no information regarding the presence of irinotecan liposome, irinotecan, or SN-38 (an active metabolite of irinotecan) in human milk, or the effects on the breastfed infant or on milk production. Irinotecan is present in rat milk [see *Data*].

Because of the potential for serious adverse reactions in breastfed infants from ONIVYDE, advise a nursing woman not to breastfeed during treatment with ONIVYDE and for one month after the last dose.

Data

Radioactivity appeared in rat milk within 5 minutes of intravenous administration of radiolabeled irinotecan HCl and was concentrated up to 65-fold at 4 hours after administration relative to plasma concentrations.

8.3 Females and Males of Reproductive Potential

Contraception

Females

ONIVYDE can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE and for seven months after the last dose.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with ONIVYDE and for four months after the last dose [see *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 264 patients who received ONIVYDE as a single agent or in combination with 5-FU and leucovorin in Study 1, 49% were ≥ 65 years old and 13% were ≥ 75 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.

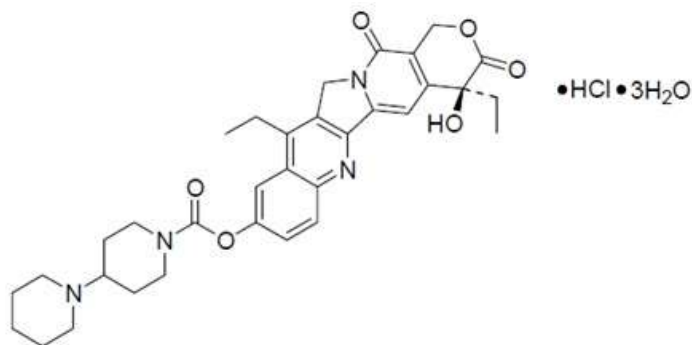
10 OVERDOSAGE

There are no treatment interventions known to be effective for management of overdose of ONIVYDE.

11 DESCRIPTION

ONIVYDE is formulated with irinotecan hydrochloride trihydrate, a topoisomerase inhibitor, into a liposomal dispersion for intravenous use. The chemical name of irinotecan hydrochloride trihydrate is (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate, monohydrochloride, trihydrate.

The empirical formula is $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$ and the molecular weight is 677.19 g/mole. The molecular structure is:



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. The liposome is a unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, which encapsulates an aqueous space containing irinotecan in a gelated or precipitated state as the sucrose octasulfate salt. The vesicle is composed of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) 6.81 mg/mL, cholesterol 2.22 mg/mL, and methoxy-terminated polyethylene glycol (MW 2000)-distearoylphosphatidyl ethanolamine (MPEG-2000-DSPE) 0.12 mg/mL. Each mL also contains 2-[4-(2-hydroxyethyl) piperazin-1-yl]ethanesulfonic acid (HEPES) as a buffer 4.05 mg/mL and sodium chloride as an isotonicity reagent 8.42 mg/mL.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Irinotecan liposome injection is a topoisomerase 1 inhibitor encapsulated in a lipid bilayer vesicle or liposome. Topoisomerase 1 relieves torsional strain in DNA by inducing single-strand breaks. Irinotecan and its active metabolite SN-38 bind reversibly to the topoisomerase 1-DNA complex and prevent re-ligation of the single-strand breaks, leading to exposure time-dependent double-strand DNA damage and cell death. In mice bearing human tumor xenografts, irinotecan liposome administered at irinotecan HCl-equivalent doses 5-fold lower than irinotecan HCl achieved similar intratumoral exposure of SN-38.

12.3 Pharmacokinetics

The plasma pharmacokinetics of total irinotecan and total SN-38 were evaluated in patients with cancer who received ONIVYDE, as a single agent or as part of combination chemotherapy, at doses between 50 and 155 mg/m² and 353 patients with cancer using population pharmacokinetic analysis.

The pharmacokinetic parameters of total irinotecan and total SN-38 following the administration of ONIVYDE 70 mg/m² as a single agent or part of combination chemotherapy are presented in Table 4.

Table 4: Summary of Mean (\pm Standard Deviation) Total Irinotecan and Total SN-38

Dose (mg/m ²)	Total Irinotecan					Total SN-38		
	C _{max} [μ g/mL] (n=25)	AUC _{0-∞} [h· μ g/mL] (n=23)	t _{1/2} [h] (n=23)	CL [L/h] (n=23)	V _d [L] (n=23)	C _{max} [ng/mL] (n=25)	AUC _{0-∞} [h·ng/mL] (n=13)	t _{1/2} [h] (n=13)
70	37.2 (8.8)	1364 (1048)	25.8 (15.7)	0.20 (0.17)	4.1 (1.5)	5.4 (3.4)	620 (329)	67.8 (44.5)

C_{max}: Maximum plasma concentration

AUC_{0- ∞} : Area under the plasma concentration curve extrapolated to time infinity

t_{1/2}: Terminal elimination half-life

CL: Clearance

V_d: Volume of distribution

Over the dose range of 50 to 155 mg/m², the C_{max} and AUC of total irinotecan increases with dose. Additionally, the C_{max} of total SN-38 increases proportionally with dose; however, the AUC of total SN-38 increases less than proportionally with dose.

Distribution

Direct measurement of irinotecan liposome showed that 95% of irinotecan remains liposome-encapsulated, and the ratios between total and encapsulated forms did not change with time from 0 to 169.5 hours post-dose. The mean volume of distribution is summarized in Table 4.

Plasma protein binding is <0.44% of the total irinotecan in ONIVYDE.

Elimination

Metabolism

The metabolism of irinotecan liposome has not been evaluated. Irinotecan is subject to extensive metabolic conversion by various enzyme systems, including esterases to form the active metabolite SN-38, and UGT1A1 mediating glucuronidation of SN-38 to form the inactive glucuronide metabolite SN-38G. Irinotecan can also undergo CYP3A4-mediated oxidative metabolism to several inactive oxidation products, one of which can be hydrolyzed by carboxylesterase to release SN-38. In the population pharmacokinetic analysis using the results of a subset with UGT1A1*28 genotypic testing, in which the analysis adjusted for the lower dose administered to patients homozygous for the UGT1A1*28 allele, patients homozygous (N=14) and non-homozygous (N=244) for this allele had total SN-38 average steady-state concentrations of 1.06 and 0.95 ng/mL, respectively.

Excretion

The disposition of ONIVYDE has not been elucidated in humans. Following administration of irinotecan HCl, the urinary excretion of irinotecan is 11 to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide), over a period of 48 hours following administration of irinotecan HCl in two patients, ranged from approximately 25% (100 mg/m²) to 50% (300 mg/m²).

Specific Populations

Age, Gender, and Renal Impairment:

The population pharmacokinetic analysis suggests that age (28 to 87 years) had no clinically meaningful effect on the exposure of irinotecan and SN-38.

The population pharmacokinetic analysis suggests that gender (196 males and 157 females) had no clinically meaningful effect on the exposure of irinotecan and SN-38 after adjusting for body surface area (BSA).

In a population pharmacokinetic analysis, mild-to-moderate renal impairment had no effect on the exposure of total SN-38 after adjusting for BSA. The analysis included 68 patients with moderate (CLcr 30 - 59 mL/min) renal impairment, 147 patients with mild (CLcr 60 - 89 mL/min) renal impairment, and 135 patients with normal renal function (CLcr > 90 mL/min). There was insufficient data in patients with severe renal impairment (CLcr < 30 mL/min) to assess its effect on pharmacokinetics.

Ethnicity: The population pharmacokinetic analysis suggests that Asians (East Asians, N=150) have 56% lower total irinotecan average steady state concentration and 8% higher total SN-38 average steady state concentration than Whites (N=182).

Hepatic Impairment: The pharmacokinetics of irinotecan liposome have not been studied in patients with hepatic impairment. In a population pharmacokinetic analysis, patients with baseline bilirubin concentrations of 1-2 mg/dL (N=19) had average steady state concentrations for total SN-38 that were increased by 37% compared to patients with baseline bilirubin concentrations of <1 mg/dL (N=329); however, there was no effect of elevated ALT/AST concentrations on total SN-38 concentrations. No data are available in patients with bilirubin >2 mg/dL.

Drug Interactions

In a population pharmacokinetic analysis, the pharmacokinetics of total irinotecan and total SN-38 were not altered by the co-administration of fluorouracil/leucovorin.

Following administration of irinotecan HCl, dexamethasone, a moderate CYP3A4 inducer, does not alter the pharmacokinetics of irinotecan.

In vitro studies indicate that irinotecan, SN-38 and another metabolite, aminopentane carboxylic acid (APC), do not inhibit cytochrome P-450 isozymes.

12.5 Pharmacogenomics

Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia from irinotecan HCl. In Study 1, patients homozygous for the UGT1A1*28 allele (N=7) initiated ONIVYDE at a reduced dose of 50 mg/m² in combination with 5-FU/LV. The frequency of Grade 3 or 4 neutropenia in these patients [2 of 7 (28.6%)] was similar to the frequency in patients not homozygous for the UGT1A1*28 allele who received a starting dose of ONIVYDE of 70 mg/m² [30 of 110 (27.3%)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of irinotecan liposome for carcinogenicity, genotoxicity or impairment of fertility. Intravenous administration of irinotecan hydrochloride to rats once weekly for 13 weeks followed by a 91-week recovery period resulted in a significant linear trend between irinotecan HCl dosage and the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas. Irinotecan HCl was clastogenic both in vitro (chromosome aberrations in Chinese hamster ovary cells) and in vivo (micronucleus test in mice). Neither irinotecan nor its active metabolite, SN-38, was mutagenic in the in vitro Ames assay.

Dedicated fertility studies have not been performed with irinotecan liposome injection. Atrophy of male and female reproductive organs was observed in dogs receiving irinotecan liposome injection every 3 weeks at doses equal to or greater than 15 mg/kg, (approximately 3 times the clinical exposure of irinotecan following administration to ONIVYDE dosed at 70 mg/m²) for a total of 6 doses. No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of irinotecan HCl in doses of up to 6 mg/kg/day to rats; however, atrophy of male reproductive organs was observed after multiple daily irinotecan HCl doses both in rodents at 20 mg/kg (approximately 0.007 times the clinical irinotecan exposure following ONIVYDE administration at 70 mg/m²) and in dogs at 0.4 mg/kg (0.0007 times the clinical exposure to irinotecan following administration of ONIVYDE).

14 CLINICAL STUDIES

The efficacy of ONIVYDE was evaluated in Study 1, a three-arm, randomized, open-label trial in patients with metastatic pancreatic adenocarcinoma with documented disease progression, after gemcitabine or gemcitabine-based therapy. Key eligibility criteria included Karnofsky Performance Status (KPS) ≥ 70 , serum bilirubin within institution limits of normal, and albumin ≥ 3.0 g/dL. Patients were randomized to receive ONIVYDE plus fluorouracil/leucovorin (ONIVYDE/5-FU/LV), ONIVYDE, or fluorouracil/leucovorin (5-FU/LV). Randomization was stratified by ethnicity (White vs. East Asian vs. other), KPS (70-80 vs. 90-100), and baseline albumin level (≥ 4 g/dL vs. 3.0-3.9 g/dL). Patients randomized to ONIVYDE/5-FU/LV received ONIVYDE 70 mg/m² as an intravenous infusion over 90 minutes, followed by leucovorin 400 mg/m² intravenously over 30 minutes, followed by fluorouracil 2400 mg/m² intravenously over 46 hours, every 2 weeks. The ONIVYDE dose of 70 mg/m² is based on irinotecan free base (equivalent to 80 mg/m² of irinotecan as the hydrochloride trihydrate). Patients randomized to ONIVYDE as a single agent received ONIVYDE 100 mg/m² as an intravenous infusion over 90 minutes every 3 weeks. Patients randomized to 5-FU/LV received leucovorin 200 mg/m² intravenously over 30 minutes, followed by fluorouracil 2000 mg/m² intravenously over 24 hours, administered on Days 1, 8, 15 and 22 of a 6-week cycle. Patients homozygous for the UGT1A1*28 allele initiated ONIVYDE at a reduced dose (50 mg/m² ONIVYDE, if given with 5-FU/LV or 70 mg/m² ONIVYDE as a single agent). 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%. Treatment continued until disease progression or unacceptable toxicity.

The major efficacy outcome measure was overall survival (OS) with two pair-wise comparisons: ONIVYDE versus 5-FU/LV and ONIVYDE/5-FU/LV versus 5-FU/LV. Additional efficacy outcome measures were progression-free survival (PFS) and objective response rate (ORR). Tumor status assessments were conducted at baseline and every 6 weeks thereafter. The trial was initiated as a two-arm study and amended after initiation to include a third arm (ONIVYDE/5-FU/LV). The comparisons between the ONIVYDE/5-FU/LV and the 5-FU/LV arms are limited to patients enrolled in the 5-FU/LV arm after this protocol amendment.

Four hundred seventeen patients were randomized to: ONIVYDE/5-FU/LV (N=117), ONIVYDE (N=151), or 5-FU/LV (N=149). Baseline demographics and tumor characteristics for the 236 patients randomized to ONIVYDE/5-FU/LV or 5-FU/LV (N=119) after the addition of the third arm to the study were a median age of 63 years (range 34-81 years) and with 41% \geq 65 years of age; 58% were men; 63% were White, 30% were Asian, 3% were Black or African American, and 5% were other. Mean baseline albumin level was 3.97 g/dL, and baseline KPS was 90-100 in 53% of patients. Disease characteristics included liver metastasis (67%) and lung metastasis (31%). A total of 13% of patients received gemcitabine in the neoadjuvant/adjuvant setting only, 55% of patients had 1 prior line of therapy for metastatic disease, and 33% of patients had 2 or more prior lines of therapy for metastatic disease. All patients received prior gemcitabine (alone or in combination with another agent), 54% received prior gemcitabine in combination with another agent, and 13% received prior gemcitabine in combination with nab-paclitaxel.

Study 1 demonstrated a statistically significant improvement in overall survival for the ONIVYDE/5-FU/LV arm over the 5-FU/LV arm as summarized in Table 5 and Figure 1.

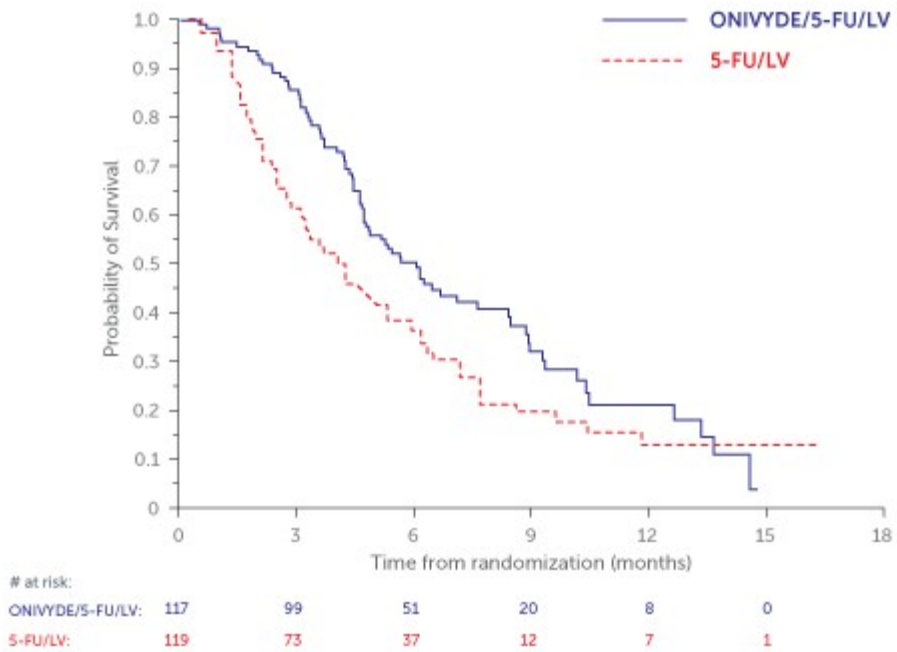
There was no improvement in overall survival for the ONIVYDE arm over the 5-FU/LV arm (hazard ratio=1.00, p-value=0.97 (two-sided log-rank test)).

Table 5: Efficacy Results from Study 1[†]

	ONIVYDE/5-FU/LV (N=117)	5-FU/LV (N=119)
Overall Survival		
Number of Deaths, n (%)	77 (66)	86 (72)
Median Overall Survival (months)	6.1	4.2
(95% CI)	(4.8, 8.5)	(3.3, 5.3)
Hazard Ratio (95% CI)	0.68 (0.50, 0.93)	
p-value (log-rank test)	0.014	
Progression-Free Survival		
Death or Progression, n (%)	83 (71)	94 (79)
Median Progression-Free Survival (months)	3.1	1.5
(95% CI)	(2.7, 4.2)	(1.4, 1.8)
Hazard Ratio (95% CI)	0.55 (0.41, 0.75)	
Objective Response Rate		
Confirmed Complete or Partial Response n (%)	9 (7.7%)	1 (0.8%)

[†] 5-FU/LV=5-fluorouracil/leucovorin; CI=confidence interval

Figure 1: Overall Survival



15 REFERENCES

1. OSHA Hazardous Drugs. *OSHA*. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ONIVYDE is available in a single-dose vial containing 43 mg irinotecan free base at a concentration of 4.3 mg/mL

NDC: 15054-0043-1

Storage and Handling

Store ONIVYDE at 2°C to 8°C (36°F to 46°F). Do NOT freeze. Protect from light.

ONIVYDE is a cytotoxic drug. Follow applicable special handling and disposal procedures.¹

17 PATIENT COUNSELING INFORMATION

Advise patients of the following:

Severe Neutropenia

Advise patients of the risk of neutropenia leading to severe and life-threatening infections and the need for monitoring of blood counts. Instruct patients to contact their healthcare provider immediately if experiencing signs of infection, such as fever, chills, dizziness, or shortness of breath [see *Warnings and Precautions (5.1)*].

Severe Diarrhea

Inform patients of the risk of severe diarrhea. Advise patients to contact their healthcare provider if they experience persistent vomiting or diarrhea; black or bloody stools; or symptoms of dehydration such as lightheadedness, dizziness, or faintness [see *Warnings and Precautions (5.2)*].

Interstitial Lung Disease

Inform patients of the potential risk of ILD. Advise patients to contact their healthcare provider as soon as possible for new onset cough or dyspnea [see *Interstitial Lung Disease (5.3)*].

Hypersensitivity to irinotecan HCl or ONIVYDE

Advise patients of the potential risk of severe hypersensitivity and that ONIVYDE is contraindicated in patients with a history of severe allergic reactions with irinotecan HCl or ONIVYDE. Instruct patients to seek immediate medical attention for signs of severe hypersensitivity reaction such as chest tightness; shortness of breath; wheezing; dizziness or faintness; or swelling of the face, eyelids, or lips [see *Contraindications (4) and Warnings and Precautions (5.4)*].

Females and males of reproductive potential

Embryo-fetal toxicity: Inform females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment and for seven months after the last dose, and to inform their healthcare provider of a known or suspected pregnancy [*see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)*].

Contraception: Advise male patients with female partners of reproductive potential to use condoms during treatment with ONIVYDE and for four months after the last dose [*see Females and Males of Reproductive Potential (8.3)*].

Lactation

Advise women not to breastfeed during treatment with ONIVYDE and for one month after the last dose [*see Use in Special Populations (8.2)*].

Manufactured for:

Ipsen Biopharmaceuticals, Inc. Cambridge, MA 02142

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