PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr ONIVYDE®*

Irinotecan Liposome for Injection

Suspension for injection

4.3 mg/mL irinotecan (as sucrose octasulfate salt)

Intravenous

Antineoplastic Agent

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RECENT MAJOR LABEL CHANGES

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4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	05/2025
7 WARNINGS AND PRECAUTIONS, 7.1.10 Acute Infusion and related reactions	08/2023
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ONIVYDE (irinotecan liposome for injection) is indicated for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), in adult patients who have disease progression following gemcitabine-based therapy.

DO NOT SUBSTITUTE ONIVYDE for or with other drug products containing irinotecan (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 4 DOSAGE AND ADMINISTRATION, and 7 WARNINGS AND PRECAUTIONS, General, Other formulations of irinotecan).

ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas.

ONIVYDE should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

1.1 Pediatrics (< 18 years of age)

Onivyde is not indicated in pediatric patients <18 years of age. Safety and effectiveness of ONIVYDE have not been established in this population.

1.2 Geriatrics (≥ 65 years of age)

Overall, no major clinical differences in safety or efficacy were reported between patients ≥ 65 years and patients < 65 years in the NAPOLI-1 study. However, a higher frequency of discontinuation (14.8% vs 7.9%) was noted in patients ≥ 65 years treated with ONIVYDE+5-FU/LV and in some cases the adverse reactions did not resolve.
Patients > 75 years experienced more frequent serious adverse reactions, dose delay, dose reduction and discontinuation compared to patients ≤ 75 years when treated with ONIVYDE + 5-FU/LV.

2 CONTRAINDICATIONS

- ONIVYDE is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE or non-liposomal irinotecan, and patients who are hypersensitive to ONIVYDE, irinotecan or to any other ingredients in the formulation or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- ONIVYDE is contraindicated during breast-feeding (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Breast-feeding).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Early diarrhea may be accompanied by cholinergic symptoms which may be prevented or ameliorated by atropine. Late diarrhea can be life threatening and should be treated promptly with loperamide (or equivalent). Monitor patients with diarrhea and give fluid and electrolytes as needed. Institute antibiotic therapy if patients develop ileus, fever, or severe neutropenia (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal and 8 ADVERSE REACTIONS).

Interrupt and reduce subsequent doses if severe diarrhea occurs (see 4 DOSAGE AND ADMINISTRATION, Dosage Modifications for Adverse Reactions, Table 1).

Severe myelosuppression may occur (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

ONIVYDE (irinotecan liposome for injection) is not equivalent to non-liposomal irinotecan formulations and should not be interchanged (see 7 WARNINGS AND PRECAUTIONS, General, Other Formulations of Irinotecan).

DO NOT SUBSTITUTE ONIVYDE FOR OR WITH OTHER IRINOTECAN FORMULATIONS.

ONIVYDE (irinotecan liposome for injection) should be administered only under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- ONIVYDE (irinotecan liposome for injection) is indicated for the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-FU and LV, in adult patients with disease progression following gemcitabine-based therapy.
- DO NOT SUBSTITUTE ONIVYDE for or with other drug products containing irinotecan.
- Dilute ONIVYDE prior to administration.
- Do not use any in-line filters.
- Discard any unused portion.
- Each single use 10 mL vial of ONIVYDE (irinotecan liposome for injection) contains the equivalent of 43 mg irinotecan free base at a concentration of 4.3 mg/mL.
- Although irinotecan is present in the form of the sucrose octasulfate salt within ONIVYDE, the following information is based upon the dose of irinotecan free base that is recommended for administration.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose
Administer ONIVYDE 70 mg/m^2 by intravenous infusion over 90 minutes, followed by LV 400 mg/m^2 intravenously over 30 minutes, followed by 5-FU 2400 mg/m^2 intravenously over 46 hours, every 2 weeks.

A reduced starting dose of ONIVYDE of 50 mg/m^2 for patients known to be homozygous for the UGT1A1*28 allele is recommended. Patients without drug related toxicities during the first 2 weeks of therapy may have their dose increased to 70 mg/m^2 based on individual patient tolerance.

Pediatrics (< 18 years old)
Health Canada has not authorized an indication for pediatric use.

Hepatic Impairment
No dedicated hepatic impairment study has been conducted with ONIVYDE. The use of ONIVYDE should be avoided in patients with bilirubin > 2.0 mg/dl, or aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 2.5 times upper limit of normal (ULN) or > 5 times ULN if liver metastasis is present.

Renal Impairment
No dedicated renal impairment study has been conducted with ONIVYDE. No dose adjustment is recommended in patients with mild to moderate renal impairment. ONIVYDE is not recommended for use in patients with severe renal impairment (CLcr <30 mL/min).

Premedication
Premedicate at least 30 minutes prior to each dose of ONIVYDE infusion with the following:
- Corticosteroid (dexamethasone or equivalent) with standard doses
- 5-HT3 receptor antagonist (or other anti-emetic) at standard dose

Dose Modifications for Adverse Reactions
For detailed dose and schedule modifications of 5-FU or LV, refer to the current relevant Product Monograph.

Table 1. Recommended Dose Modifications for ONIVYDE + 5-FU/LV[*]

Toxicity **NCI CTC Grade[†]** (Value)	**Occurrence**	**ONIVYDE/5-FU** **Adjustment[‡]**
Neutropenia	A new cycle of therapy should not begin until the absolute neutrophil count is ≥1500/mm^3	
Grade 3 or 4 (<1000/mm^3) **or neutropenic fever**	**First**	Reduce ONIVYDE dose to 50 mg/m^2 Reduce 5-FU dose by 25%.
	Second	Reduce ONIVYDE dose to 43 mg/m^2 Reduce 5-FU dose by an additional 25%
	Third	Discontinue treatment
Other hematological toxicities (thrombocytopenia and leukopenia)	A new cycle of therapy should not begin until the platelet count is ≥100,000/mm^3 Dose modifications for leukopenia and thrombocytopenia are based on NCI toxicity grading and are the same as recommended for neutropenia above.	

Diarrhea	A new cycle of therapy should not begin until diarrhea resolves to ≤ Grade 1 (2-3 stools/day more than pre-treatment frequency).	
Grade 3 or 4 (7-9 stools/day > pretreatment) or (>10 stools/day > pretreatment)	**First**	Reduce ONIVYDE dose to 50 mg/m^2 Reduce 5-FU dose by 25%
	Second	Reduce ONIVYDE dose to 43 mg/m^2 Reduce 5-FU dose by an additional 25%
	Third	Discontinue treatment
Nausea/vomiting	A new cycle of therapy should not begin until nausea/vomiting resolves to ≤ Grade 1 or baseline	
Grade 3 or 4 despite antiemetic therapy	**First**	**Optimize antiemetic therapy** Reduce ONIVYDE dose to 50 mg/m^2
	Second	**Optimize antiemetic therapy** Reduce ONIVYDE dose to 43 mg/m^2
	Third	Discontinue treatment
Interstitial lung disease**	**First**	Discontinue treatment
Other nonhematological toxicities‡ **Grade 3 or 4**	**First**	Reduce ONIVYDE dose to 50 mg/m^2 Reduce 5-FU dose by 25%
	Second	Reduce ONIVYDE dose to 43 mg/m^2 Reduce 5-FU dose by an additional 25%
	Third	Discontinue treatment

* For patients who start treatment with 50 mg/m^2 ONIVYDE and do not dose escalate to 70 mg/m^2, the recommended first dose reduction is to 43 mg/m^2 and the second dose reduction is to 35 mg/m^2. Patients who require further dose reduction should discontinue treatment.
** Including pneumonitis
† National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0
‡ Excludes asthenia and anorexia. Asthenia and Grade 3 anorexia do not require dose adjustment.

4.3 Reconstitution

ONIVYDE is a cytotoxic drug. Follow applicable special handing and disposable procedures.

Preparation
Dilute using a needle not larger than 21 gauge with 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP, to prepare a suspension of the appropriate dose of ONIVYDE diluted to a final volume of 500mL. Mix diluted suspension by gentle inversion.

Storage of Diluted Suspensions
Room temperature: Diluted suspension should be used immediately, but may be stored at ambient temperature (approximately 25ºC) for up to 4 hours prior to infusion when protected from light.

Refrigeration: Diluted suspension can be stored in the refrigerator at 2ºC to 8ºC (36ºF to 46ºF) for no more than 24 hours prior to use. Allow diluted suspension to come to room temperature (approximately 25ºC) prior to administration. Protect from light. Do NOT freeze. See 11 STORAGE, STABILITY AND DISPOSAL.

Table 2 – Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Concentration per mL

10 mL	490 mL	500 mL	0.086 mg/mL

4.4 Administration

Do not use any in-line filters. Discard any unused portion.

5 OVERDOSAGE

There is no known antidote for overdosage of ONIVYDE. Interrupt ONIVYDE and institute supportive care to prevent dehydration due to diarrhea and to treat any infectious complications.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Suspension for Injection / 43 mg/10 mL (4.3 mg per mL)	1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid (HEPES), cholesterol, N-(carbonyl-methoxypolyethlyene glycol-2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-2000-DSPE), sodium chloride, sucrose octasulfate, water for injection

ONIVYDE is a sterile, white to slightly yellow opaque isotonic liposomal dispersion concentrate. Each 10 mL vial contains the equivalent of 43 mg irinotecan at a concentration of 4.3 mg/mL (as sucrose octasulfate salt).

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Other Formulations of Irinotecan

ONIVYDE is a liposomal formulation of irinotecan with different pharmacokinetic properties compared to non-liposomal irinotecan. The dose concentration and strength are different in comparison to non-liposomal irinotecan formulations.

Prior Irinotecan Exposure

Due to the limited number of patients with prior exposure to non-liposomal irinotecan, the benefit of ONIVYDE has not been established.

Cardiovascular
Onivyde has been associated with thromboembolic events such as pulmonary embolism, venous thrombosis and arterial thromboembolism. A thorough medical history should be obtained in order to identify patients with multiple risk factors in addition to the underlying neoplasm. Patients should be informed about the signs and symptoms of thromboembolism and advised to contact their physician or nurse immediately if any such signs or symptoms should occur.

Gastrointestinal
Diarrhea
Diarrhea can occur with ONIVYDE treatment. In the NAPOLI-1 study, Grade 3 or 4 diarrhea occurred in 15 out of 117 patients (12.8%) receiving ONIVYDE + 5-FU/LV. The frequency was higher in Caucasian patients than in Asian patients (Grade 3 or higher diarrhea 19% vs 3%, respectively) when treated with ONIVYDE + 5-FU/LV.

Early Onset
Early onset diarrhea, typically appearing during or shortly after treatment, can occur but is infrequent and usually transient.

Administer intravenous or subcutaneous atropine 0.25 to 1 mg (unless clinically contraindicated) for early onset diarrhea. Interrupt and reduce, as appropriate, subsequent doses if severe diarrhea occurs (see 4 DOSAGE AND ADMINISTRATION, Dose Modifications for Adverse Reactions, Table 1. Recommended Dose Modifications for ONIVYDE + 5-FU/LV).

Late Onset
Late onset diarrhea, typically appearing more than 24 hours after treatment, can be debilitating and, on rare occasions, life threatening since persistent loose or watery stools can result in dehydration, electrolyte imbalance or sepsis. Diarrhea may be complicated by colitis, ulceration, bleeding ileus, colon obstruction, and infection. For patients experiencing late diarrhea, the median time to late diarrhea onset was 8 days from the previous dose of ONIVYDE.

Initiate loperamide at first occurrence of poorly formed or loose stools or at the earliest onset of bowel movements more frequent than normal and give until patient is without diarrhea for at least 12 hours. Loperamide should not be used for more than 48 consecutive hours due to risk of paralytic ileus. If diarrhea persists more than 48 hours, stop loperamide, monitor and replace fluid electrolytes and continue antibiotic support until resolution for accompanying symptoms. If diarrhea persists while patient is on loperamide for more than 24 hours, consider adding oral antibiotic support (fluoroquinolone for 7 days). There is theoretical potential of fluroquinolone-ONYVIDE drug-drug interaction (See 9 DRUG INTERACTIONS, Drug-Drug Interactions, Table 6. Established or Potential Drug-Drug Interactions for Non-Liposomal Irinotecan).

Withhold ONIVYDE for Grade 2-4 diarrhea. Delay ONIVYDE treatment until diarrhea resolves to ≤ Grade 1 (2-3 stools/day more than pre-treatment frequency). Do not administer ONIVYDE to patients with bowel obstruction, until it is resolved. Following Grade 3 or 4 diarrhea, the subsequent dose of ONIVYDE and 5-FU should be reduced (see 4 DOSAGE AND ADMINISTRATION, Dose Modifications for Adverse Reactions, Table 1. Recommended Dose Modifications for ONIVYDE + 5-FU/LV).

Hematologic

Myelosuppression / Neutropenia

Death due to sepsis following neutropenia has been reported in patients treated with ONIVYDE. In the pivotal Phase 3 study – NAPOLI-1, neutropenic fever/sepsis (defined as febrile neutropenia or neutropenic sepsis) occurred in 4 out of 117 patients (3.4%) receiving ONIVYDE plus 5-FU/LV (ONIVYDE + 5-FU/LV). Withhold treatment if neutropenic fever occurs or the absolute neutrophil count drops below 1500/mm^3. Manage neutropenic fever promptly with antibiotic support. Resume treatment after recovery to an absolute neutrophil count ≥ 1500/mm^3 at reduced doses.

The frequency of Grade 3 or 4 neutropenia was higher in Asian patients (18 out of 33 [55%]) than in Caucasian patients (13 out of 73 [18%]) when treated with ONIVYDE + 5-FU/ LV. Neutropenic fever/sepsis was reported in 2 of 33 (6.1%) Asian patients versus 1 of 73 (1.4%) Caucasian patients.

Patients with baseline serum total bilirubin levels of greater than 2 mg/dL were excluded from ONIVYDE clinical trials. Patients with deficient glucuronidation of bilirubin, such as those with Gilbert's syndrome, may be at greater risk of myelosuppression when receiving therapy with ONIVYDE. Any consideration of a dose reduction is at the discretion of the treating physician (see 4 DOSAGE AND ADMINISTRATION, Dose Modifications for Adverse Reactions, Table 1. Recommended Dose Modifications for ONIVYDE + 5-FU/LV).

Risk of Neutropenia in Patients with Homozygous UGT1A1 Activity

Individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7 / 7 genotype) have an increased risk for developing neutropenia following non-liposomal irinotecan therapy. Consider a reduced starting dose of ONIVYDE of 50 mg/m^2 for patients known to be homozygous for the UGT1A1*28 allele. For patients who start treatment with 50 mg/m^2 ONIVYDE and do not have their dose escalated to 70 mg/m^2, the recommended first dose reduction is to 43 mg/m^2 and the second dose reduction is to 35 mg/m^2. Patients who require further dose reduction should discontinue treatment. Patients without drug related toxicities during the first 2 weeks of therapy may have their dose of ONIVYDE increased to 70 mg/m^2 based on individual patient tolerance.

In NAPOLI-1 Study, patients homozygous for the UGT1A1*28 allele did not experience a greater incidence of Grade 3 or 4 neutropenia than those not homozygous (2 out of 7 patients [28.6%] vs 30 of 110 patients [27.3%], respectively) (see 4 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

Neurologic

Cholinergic Reactions

Early onset diarrhea may also be accompanied by cholinergic symptoms that can include rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis and intestinal hyperperistalsis that can induce abdominal cramping. In NAPOLI-1 study, early onset diarrhea (diarrhea onset within 24 hours of ONIVYDE administration) occurred in 35 patients (30%) and cholinergic events occurred in 4 patients (3.4%) receiving ONIVYDE + 5-FU/LV. Consider prophylactic or therapeutic treatment with atropine in patients experiencing cholinergic symptoms (0.25 mg to 1 mg, administered intravenously or subcutaneously), unless contraindicated. No late onset cholinergic events were observed.

Respiratory

Interstitial Lung Disease

Interstitial Lung Disease (ILD)-like events leading to fatalities have occurred in patients receiving non-liposomal irinotecan. Post-market cases and clinical trial cases of ILD and pneumonitis have been reported in patients receiving ONIVYDE. Risk factors include pre-existing lung disease, use of pneumotoxic medicinal products, colony stimulating factors or having previously received radiation therapy. Patients with risk factors should be closely monitored for respiratory symptoms before and during ONIVYDE therapy. A reticulo-nodular pattern on chest X-ray was observed in a small percentage of patients enrolled in a clinical study with non-liposomal irinotecan. New or progressive dyspnea, cough, and fever should prompt interruption of ONIVYDE treatment, pending diagnostic evaluation. ONIVYDE should be discontinued in patients with a confirmed diagnosis of ILD (see Table 1 Dose Modifications).

7.1 Special Populations

7.1.1 Pregnant Women

There are no human data on the use of ONIVYDE in pregnant women. ONIVYDE can cause harm to the fetus when administered to a pregnant woman based on its mechanism of action and findings in animals, where non-liposomal irinotecan was teratogenic and caused embryo-fetal toxicity in rats and rabbits. ONIVYDE is therefore not recommended during pregnancy (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicity).

If ONIVYDE is used during pregnancy, or if a patient becomes pregnant while receiving therapy, inform the patient of the potential hazard to the fetus and the potential risk for loss of the pregnancy.

7.1.2 Breast-feeding

It is unknown whether ONIVYDE or its metabolites are excreted into human milk. Because of the potential for serious adverse reactions of ONIVYDE in breast-feeding infants, ONIVYDE is contraindicated during breast-feeding. Patients should not breast-feed until one month after the last dose (See 10 CLINICAL PHARMACOLOGY, Detailed Pharmacology).

7.1.3 Pediatrics

Onivyde is not indicated in pediatric patients <18 years of age. Safety and effectiveness of ONIVYDE have not been established in this population.

7.1.4 Geriatrics

Overall, no major clinical differences in safety or efficacy were reported between patients ≥ 65 years and patients < 65 years in the NAPOLI-1 study. However, a higher frequency of discontinuation (14.8% vs 7.9%) was noted in patients ≥ 65 years treated with ONIVYDE+5-FU/LV and in some cases the adverse reactions did not resolve.
Patients > 75 years experienced more frequent serious adverse reactions, dose delay, dose reduction and discontinuation compared to patients ≤ 75 years when treated with ONIVYDE + 5-FU/LV.

7.1.5 Immunosuppressive effects and vaccines

Administration of live or live-attenuated vaccines in patients immunocompromised by cancer chemotherapeutic medicinal products including ONIVYDE may result in serious or fatal infections; therefore vaccination with a live vaccine should be avoided. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished (see 8 ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Table 4).

7.1.6 Interactions with strong CYP3A4 inducers

ONIVYDE should not be administered with strong CYP3A4 inducers such as anticonvulsants (phenytoin, phenobarbital or carbamazepine), rifampin, rifabutin and St. John's Wort unless there are no therapeutic alternatives. The appropriate starting dose for patients taking these anticonvulsants or other strong inducers has not been defined. Consideration should be given to substituting with non-enzyme inducing therapies at least 2 weeks prior to initiation of ONIVYDE therapy (See 9 DRUG INTERACTIONS, Drug-Drug Interactions, Strong CYP3A4 Inducers and Table 6. Established or Potential Drug-Drug Interactions for Non-Liposomal Irinotecan).

7.1.7 Interactions with strong and moderate CYP3A4 inhibitors or strong UGT1A1 inhibitors

ONIVYDE should not be administered with strong CYP3A4 inhibitors (e.g. clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole, grapefruit juice). Strong CYP3A4 inhibitors should be discontinued at least 1 week prior to starting ONIVYDE therapy (see 9 DRUG INTERACTIONS, Drug-Drug Interactions, Strong CYP3A4 or UGT1A1 Inhibitors and Table 6. Established or Potential Drug-Drug Interactions for Non-Liposomal Irinotecan).

Although no dedicated drug interaction studies have been conducted, the established or potential drug-drug interactions should be similar to those seen with non-liposomal irinotecan. Fluoroquinolone antibiotics (ciprofloxacin, norfloxacin) and macrolide antibiotics (azithromycin, clarithromycin, erythromycin) are moderate CYP3A4 inhibitors. For the indicated patient population, the risk and benefit of using concomitant medicines that are moderate CYP3A4 inhibitors should be evaluated and monitored (see 9 DRUG INTERACTIONS, Drug-Drug Interactions, Table 6 Established or Potential Drug-Drug Interactions for Non-Liposomal Irinotecan).

ONIVYDE should not be administered with strong UGT1A1 inhibitors (e.g. atazanavir, gemfibrozil, indinavir) unless there are no therapeutic alternatives (See 9 DRUG INTERACTIONS, Drug-Drug Interactions, Strong CYP3A4 or UGT1A1 Inhibitors and Table 6 Established or Potential Drug-Drug Interactions for Non-Liposomal Irinotecan).

7.1.8 Patients with hepatic impairment

No dedicated hepatic impairment study has been conducted with ONIVYDE. The use of ONIVYDE should be avoided in patients with bilirubin > 2.0 mg/dl, or aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 2.5 times upper limit of normal (ULN) or > 5 times ULN if liver metastasis is present (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency).

7.1.9 Patients with renal impairment

No dedicated renal impairment study has been conducted with ONIVYDE. No dose adjustment is recommended in patients with mild to moderate renal impairment. ONIVYDE is not recommended for use in patients with severe renal impairment (CL_{cr} <30 mL/min) (see 10 ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency).

7.1.10 Acute infusion and related reactions

Infusion reactions primarily consisting of rash, urticaria, periorbital edema or pruritus were reported in patients receiving ONIVYDE treatment. New events (all grade 1 or grade 2) occurred generally early during ONIVYDE treatment, with only 2 out of 10 patients noted with events after the fifth dose. Hypersensitivity reactions, including anaphylactic/anaphylactoid reaction and angioedema may occur. ONIVYDE should be discontinued in case of severe hypersensitivity reactions (See 8 ADVERSE REACTIONS, Clinical Trial Adverse Reactions, Infusion Reaction).

7.1.11 Underweight patients (body mass index < 18.5 kg/m^2)

In the clinical study evaluating ONIVYDE + 5-FU/LV, 5 of 8 underweight patients experienced a Grade 3 or 4 adverse reactions, mostly myelosuppression, while 7 of the 8 patients required dose modification such as dose delay, dose reduction or dose discontinuation. Caution should be exercised when using ONIVYDE in patients with body mass index < 18.5 kg/m^2.

7.1.12 Prior Whipple procedure

Patients with a history of a Whipple procedure have a higher risk of serious infections following ONIVYDE in combination with 5-FU and LV. Patients should be monitored for signs of infections.

7.1.13 Females and Males of Reproductive Potential

Prior to starting the administration of ONIVYDE pegylated liposomal consider advising patients on the preservation of gametes.

Pregnancy Testing
Perform pregnancy testing in women of childbearing potential prior to starting treatment with ONIVYDE and intermittently during treatment with ONIVYDE.

Contraception
Females
ONIVYDE can cause fetal harm. Advise females of reproductive potential to avoid becoming pregnant while taking ONIVYDE. Advise sexually active females of reproductive potential to use effective contraception while taking ONIVYDE and for 7 months after the last dose of ONIVYDE. Advise patients to contact their healthcare professional if they become pregnant, or if pregnancy is suspected, while taking ONIVYDE.

Males

Advise sexually active men to use condoms while on treatment and for at least four months after their last dose of ONIVYDE.

7.1.14 Monitoring and Laboratory Tests

There are risks of neutropenia leading to severe and life-threatening infections and need periodic monitoring of blood counts. Hematologic evaluation of patients must be performed at baseline and prior to every dose of ONIVYDE. Before the first administration of ONIVYDE, the absolute neutrophil count (ANC) should be ≥ 1.5 x 10^9/L, the platelet count ≥ 100 x 10^9 /L and hemoglobin ≥ 10 g/dL. Before subsequent administrations of ONIVYDE, the ANC should be ≥ 1 x 10^9 /L and the platelet count ≥ 50 x 10^9/L. Patients with evidence of compromised bone marrow depletion should be monitored closely and provided with supportive care measures when clinically indicated. Discontinue ONIVYDE in patients who experience life-threatening complications despite supportive care for bone marrow failure.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

NAPOLI-1 STUDY

The safety data described below are derived from NAPOLI-1 Study. Patients with metastatic pancreatic cancer who had been previously treated with gemcitabine-based therapy were randomized to receive intravenous ONIVYDE 70 mg/m^2 with LV 400 mg/m^2 and 5-FU 2,400 mg/m^2 over 46 hours every 2 weeks (n=117) or to intravenous ONIVYDE 100 mg/m^2 every 3 weeks (n=147) or to intravenous LV 200 mg/m^2 and 5-FU 2,000 mg/m^2 over 24 hours weekly for 4 weeks followed by 2 week rest (n=134) [See 14 CLINICAL TRIALS]. The median duration of exposure was 8.7 weeks in the ONIVYDE+5-FU/LV arm, 8.9 weeks in the ONIVYDE monotherapy arm and 6 weeks in the 5-FU/LV arm. Among patients who received study treatment, the median age was 64 years, 56% were male, 61% identified themselves as White, 32% as Asian, 3% as Black, and 4% as Other race. Most patients (99.5%) enrolled in the NAPOLI-1 study were with Karnofsky performance status (KPS) of ≥ 70.

In NAPOLI-1 Study, the most common adverse reactions observed in ONIVYDE-treated patients (incidence ≥ 20 %) were, in order of decreasing frequency, diarrhea, nausea, vomiting, decreased appetite, neutropenia, fatigue, anemia, stomatitis, alopecia, hypokalemia, weight decreased and pyrexia. The most common serious adverse reactions (incidence ≥ 2 %) were vomiting, diarrhea, neutropenia, neutropenic fever/sepsis, nausea, pyrexia, anemia, device related infection, pneumonia, sepsis, dehydration, septic shock, acute renal failure, thrombocytopenia, thrombotic events, ileus and decreased appetite.

Adverse reactions led to permanent discontinuation of all study therapy in 11% of patients receiving ONIVYDE + 5-FU/LV, 12% of patients receiving ONIVYDE monotherapy and 8% of patients receiving 5-FU/LV. The most common reasons (more than 1 patient in the ONIVYDE containing arms) for treatment discontinuation was diarrhea, vomiting, ascites

and sepsis. One death was considered treatment related (neutropenic sepsis) in the ONIVYDE + 5-FU/LV arm and four deaths were considered treatment related in the ONIVYDE monotherapy arm (gastrointestinal toxicity, disseminated intravascular coagulation/pulmonary emboli, septic shock and infectious enterocolitis). No treatment related deaths were reported in the 5-FU/LV arm.
Table 4 presents the percentage of ONIVYDE-treated patients by arm in NAPOLI-1 study experiencing an adverse reaction at a higher rate than in the 5-FU/-LV arm.

Table 4. Adverse Reactions Occurring at a Higher Incidence in either the ONIVYDE + 5-FU/LV or ONIVYDE Arm than in the 5-FU/LV Arm (Between Arm Difference of ≥ 5% [Grade 1-4]* or ≥ 2% [Grade 3 and 4]):

Adverse Reaction	ONIVYDE + 5-FU/LV N=117		ONIVYDE N=147		5-FU/LV N=134	
	Grades 1-4 (%)	Grades 3 / 4 (%)	Grades 1-4 (%)	Grades 3 / 4 (%)	Grades 1-4 (%)	Grades 3 / 4 (%)
Gastrointestinal disorders						
Diarrhea	59	13	70	21	26	5
Diarrhea, early†	30	3	15	1	15	0
Diarrhea, late‡	43	9	65	13	17	5
Vomiting	52	11	54	14	26	3
Nausea	51	8	61	5	34	3
Stomatitis§	32	4	12	0	12	1
Alanine aminotransferase increased	7	1	3	1	2	0
Blood and lymphatic system disorders						
Neutropenia¶	39	27	25	15	5	2
Anemia	38	9	33	11	23	7
Thrombocytopenia #	13	3	5	1	7	0
Thrombotic events^	5	3	13	7	8	6
Infections and infestations						
Sepsis	4	3	1	1	2	1
Neutropenic fever/sepsis♠	3	3	5	4	1	0
Gastroenteritis	3	3	2	1	0	0
Device related infection	3	3	2	2	0	0
General disorders and administration site conditions						
Fatigue	40	14	37	6	28	4
Pyrexia	23	2	20	1	11	1
Metabolism and nutrition disorders						
Decreased appetite	44	4	49	9	32	2

Weight decreased	17	2	20	1	7	0
Hypokalemia	12	3	22	11	9	2
Dehydration	8	4	10	3	7	2
Hypomagnesemia	6	0	14	3	4	1
Skin and subcutaneous tissue disorders						
Alopecia	14	1	22	0	5	0

* NCI CTCAE version 4.0 used for grading
† Early diarrhea: onset of ≤ 1 day after drug administration
‡ Late diarrhea: onset of > 1 day after drug administration
§ Includes stomatitis, aphthous stomatitis, mouth ulceration, mucosal inflammation
¶ Includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutropenic sepsis, neutrophil count decreased, pancytopenia
# Includes pancytopenia, platelet count decreased, thrombocytopenia
♠ Includes febrile neutropenia, neutropenic sepsis
^ Includes acute coronary syndrome, cerebral artery occlusion, cerebrovascular accident, deep vein thrombosis, myocardial infarction, portal vein thrombosis, pulmonary embolism, splenic vein thrombosis, sudden death, thrombophlebitis

In NAPOLI-1 Study, compared to Caucasians, Asian patients were observed with a lower incidence of diarrhea [14 (19.2%) out of 73 Caucasians had ≥ Grade 3 diarrhea, and 1 out of 33 (3.3%) Asians had ≥ Grade 3 diarrhea]. In patients receiving ONIVYDE + 5-FU/LV, the incidence of ≥ Grade 3 neutropenia was higher among Asian patients [18 of 33 (55%)] compared to Caucasian patients [13 of 73 (18%)]. Neutropenic fever/neutropenic sepsis was reported in 6% of Asian patients and 1% of Caucasian patients. This is consistent with the population pharmacokinetic analysis that showed a lower exposure to irinotecan and a higher exposure to its active metabolite SN-38 in Asians than in Caucasians (See 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Ethnic Origin).

Renal Impairment / Renal Failure: Renal impairment and acute renal failure have been identified, usually in patients who became volume depleted from severe vomiting and/or diarrhea. Acute renal failure was reported in 6 of 117 patients (5%) in the ONIVYDE + 5-FU/LV arm, 10 of 147 (7%) in the ONIVYDE monotherapy arm and 6 of 134 patients (5%) in the plus 5-FU/LV arm.

Infusion Reaction: Acute infusion reaction (allergic reaction, rash/desquamation, urticaria, periorbital edema, infusion site extravasation, pruritus) was reported in 2% of patients with advanced solid tumors who received ONIVYDE as a single agent or in combination with other therapies.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

As presented in Table 5, the following laboratory abnormalities (all Grades) occurred in ≥ 10% of ONIVYDE-treated patients.

Table 5. Any Laboratory Abnormalities Occurring at ≥ 10% and at a Higher Incidence in either the ONIVYDE + 5-FU/LV or ONIVYDE Arm than in the 5-FU/LV Arm

(Between Arm Difference of ≥ 5% [Grade 1-4][*] or ≥ 2% [Grade 3 and 4])[*]

Laboratory abnormality	ONIVYDE + 5-FU/LV[#] N=117		ONIVYDE[#] N=147		5-FU/LV[#] N=134	
	Grades 1-4 (%)	Grades 3/4 (%)	Grades 1-4 (%)	Grades 3/4 (%)	Grades 1-4 (%)	Grades 3/4 (%)
Hematology						
Hemoglobin, decreased	97	6	95	7	86	5
Lymphocyte count, decreased	81	27	77	29	75	17
Leucocyte count, decreased	67	16	50	15	20	0
Neutrophil count, decreased	52	20	36	16	6	2
Platelet count, decreased	41	2	26	1	33	0
Chemistry						
Alkaline phosphatase, increased	70	9	80	7	66	7
Alanine aminotransferase (ALT), increased	51	6	50	1	37	1
Albumin, decreased	43	2	55	1	30	0
Aspartate aminotransferase (AST), increased	39	3	43	2	38	2
Magnesium, decreased	35	0	49	3	21	0
Potassium, decreased	32	2	39	8	19	2
Calcium, decreased	32	1	23	0	20	0
Phosphate, decreased	29	4	22	3	18	1
Sodium, decreased	27	5	27	11	12	3
Creatinine, increased	18	0	12	0	13	0
Urate, increased	15	1	8	0	6	2

[*] grading of laboratory abnormalities was based on NCI CTCAE version 4.0, worst Grade shown
[#] Percentages are based on the number of patients with a baseline and at least one post-baseline measurement

8.5 Post-Market Adverse Reactions

The most frequently reported events have been diarrhea, infusion reactions, vomiting, nausea, abdominal pain, fatigue, and neutropenia.

Other adverse drug reactions reported during post-marketing experience with ONIVYDE are listed below:
Immune system disorders: anaphylactic/anaphylactoid reaction, angioedema

Skin and subcutaneous tissue disorders: erythema
Respiratory, thoracic and mediastinal disorders: Interstitial lung disease, pneumonitis

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal drug interaction studies have been conducted with ONIVYDE. ONIVYDE may interact with drugs known to interact with the conventional formulation of non-liposomal irinotecan.

9.3 Drug-Behavioural Interactions

ONIVYDE may influence a person's ability to drive and handle machines. During treatment patients should observe caution when driving or using machines.

9.4 Drug-Drug Interactions

Fluorouracil (5-FU) and Leucovorin (LV)
Based on the population pharmacokinetic analysis of ONIVYDE, the pharmacokinetics of total irinotecan and total SN-38 were not altered by the co-administration of 5-FU/LV.

Strong CYP3A4 Inducers
Following administration of non-liposomal irinotecan, 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, phenobarbital, St. John's Wort) if possible. Substitute non-enzyme inducing therapies at least 2 weeks prior to initiation of ONIVYDE therapy.

Strong CYP3A4 or UGT1A1 Inhibitors
Following administration of non-liposomal irinotecan, 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, grapefruit juice) 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.

Table 6. Established or Potential Drug-Drug Interactions for Non-LiposomalIrinotecan

	Ref[a]	Effect	Clinical Comment
CYP3A4 inhibitors Azole antifungals ketoconazole fluconazole, itraconazole	CT T	Strong CYP3A4 inhibitors increased SN-38 exposure (AUC and Cmax) by 109%	Increased systemic exposure causing toxicity. Avoid co-administration of strong CYP3A4 inhibitors.

Cimetidine Fluoroquinolone antibiotics ciprofloxacin, norfloxacin Macrolide antibiotics azithromycin, clarithromycin, erythromycin Calcium channel blockers diltiazem, verapamil, nifedipine Grapefruit juice	T T T T T	Moderate CYP3A4 inhibitors potentially increase both irinotecan and SN-38 exposure	Monitor periodically for toxicity when co-administering moderate CYP3A4 inhibitors
atazanavir sulfate	T	See atazanavir Product Monograph	
UGT1A1 inhibitors Antiretroviral HIV atazanavir, indinavir Lipid regulating agent gemfibrozil	 T T	Strong UGT1A1 inhibitors significantly increase both irinotecan and SN-38 exposure	Potential for increased systemic exposure causing toxicity. Avoid co-administration of strong UGT1A1 inhibitors.
CYP3A4 inducers Anticonvulsants carbamazepine, phenobarbital, phenytoin St John's Wort Glucocorticoids dexamethasone Anti-tuberculosis rifampin	 CT T T T	SN-38 exposure (AUC and Cmax) significantly decreased by 42%	Potential for decreased efficacy due to decreased systemic exposure. Avoid co-administration of strong CYP3A4 inducers, if possible.

[a] Level of Evidence; C = Case Study, CT = Clinical Trial, T= Theoretical
Source: Camptosar Product Monograph, December 9, 2014

9.5 Drug-Food Interactions

ONIVYDE should not be administered with grapefruit juice, a strong CYP3A4 inhibitor.

9.6 Drug-Herb Interactions

ONIVYDE interactions with herbal products have not been established. St John's Wort has been well recognized as a regulator of CYP3A4. The concomitant use of ONIVYDE with St John's Wort should therefore be monitored closely.

9.7 Drug-Laboratory Test Interactions

ONIVYDE interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

ONIVYDE is an irinotecan liposomal formulation for injection. Irinotecan, a topoisomerase 1 inhibitor, is a derivative of camptothecin that relieves torsional strain in DNA by inducing

single-strand breaks, rotating the cleaved strand around the double helix axis and re-ligating the cleaved strand to re-establish intact duplex DNA. Both irinotecan and its active metabolite SN-38 bind reversibly to the topoisomerase I-DNA complex and prevent re-ligation of these single-strand breaks. The liposome is a unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, which encapsulates an aqueous space containing irinotecan.

10.2 Detailed Pharmacology

The active ingredient in ONIVYDE is non-liposomal irinotecan, a topoisomerase 1 inhibitor, which is encapsulated in a long-circulating liposome. In animal models, ONIVYDE has been shown to extend plasma levels of irinotecan and prolong the exposure to the active metabolite SN-38 at the site of the tumor. In mice, bearing human colorectal carcinoma xenografts, longer durations of SN-38 concentrations in tumors above a minimum inhibitory concentration were associated with increased anti-tumor activity; when ONIVYDE and non-liposomal irinotecan were administered at the same dosage (35 mg/kg), ONIVYDE resulted in tumor SN-38 durations above a threshold exposure at least five times longer than non-liposomal irinotecan.

Radioactivity related to ^{14}C-irinotecan HCl crosses the placenta of rats following intravenous administration of 10 mg/kg, which in separate studies produced an irinotecan C_{max} and AUC about 3 and 0.5 times, respectively, the corresponding values in patients administered 108 mg/m^2 (as anhydrous free base).

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

10.3 Pharmacokinetics

The plasma pharmacokinetics of ONIVYDE were evaluated from pooled data of 95 patients using non-compartmental analysis, and from 353 patients using population pharmacokinetic analysis. Patients received ONIVYDE as monotherapy or as part of combination therapy at doses between 50 and 150 mg/m^2. The pharmacokinetic parameters of total irinotecan and SN-38, following the administration of ONIVYDE at 70 mg/m^2 are presented in Table 7.

Table 7. Summary of Mean (±Standard Deviation) Total Irinotecan and SN-38 Pharmacokinetic Parameters in Patients with Solid Tumors

Dose (mg/m^2) (n=25)	Total Irinotecan					SN-38		
	C_{max} [µg/mL] (n=25)	$t_{1/2}$ [h] (n=23)	$AUC_{0-\infty}$ [h·µg/mL] (n=23)	V_d [L] (n=23)	CL [L/h] (n=23)	C_{max} [ng/mL] (n=25)	$t_{1/2}$ [h] (n=13)	$AUC_{0-\infty}$ [h·ng/mL] (n=13)
70	37.2 (8.8)	25.8 (15.7)	1364 (1048)	4.1 (1.5)	0.20 (0.17)	5.4 (3.4)	67.8 (44.5)	620 (329)

C_{max}: Maximum plasma concentration
$t_{½}$: Terminal elimination half-life
$AUC_{0-\infty}$: Area under the plasma concentration curve extrapolated to time infinity
V_d: Volume of distribution

Over the dose range of 50 to 150 mg/m^2, the maximum concentrations of both total irinotecan and SN-38 increase linearly with dose. The AUC's of total irinotecan increase linearly with dose; the AUC's of SN-38 increase less than proportionally with dose. The half-lives of both total irinotecan and SN-38 do not change with dose.

Distribution
Direct measurement of liposomal irinotecan shows that 95% of irinotecan remains liposome-encapsulated during circulation and the ratios between total and encapsulated forms did not change with time from 0 to 169.5 hours post-dose. The volume of distribution of ONIVYDE 70 mg/m^2 is 4.1 L.

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

Metabolism
The metabolism of ONIVYDE has not been evaluated. UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Approximately 10% of the North American population is homozygous for the UGT1A1*28 allele (also referred to as UGT1A1 7/7 genotype). Based on the results of the population pharmacokinetic analysis, patients homozygous and non-homozygous for the UGT1A1*28 allele (UGT1A1 7 / 7 genotype) have similar SN-38 exposure. Caucasians who were homozygous had numerically higher SN-38 average concentrations than non-homozygous, but these are not statistically significant (0.81 [95%CI: 0.72-0.92; n= 23] and 0.68 [95%CI: 0.65-0.72; n= 220] ng/mL.

Elimination
The disposition of ONIVYDE has not been fully elucidated in humans.
The plasma clearance of total irinotecan from ONIVYDE 70 mg/m^2 is 0.077 L/h/m^2 with a terminal half life of 26.8 h. Following administration of irinotecan 110 mg/m^2, the plasma clearance is 13.3 L/h/m^2 with a terminal half life of 10.4 h.

Special Populations and Conditions

- **Pediatrics (<18 years of age)** No pharmacokinetic data are available in the pediatric population.
- **Age** The population pharmacokinetic analysis shows that age (28-87 yr) has no clinically meaningful effect on the exposure of ONIVYDE and SN-38
- **Sex** The population pharmacokinetic analysis shows that gender (196 [56%] males and 157 [44%] females) has no clinically meaningful effect on the exposure of ONIVYDE and SN-38 (C_{avg}: 0.85 [95%CI: 0.80-0.90] ng/mL in females and 0.73 [95%CI: 0.70-0.77] ng/mL in males) after adjusting for body surface area (BSA).
- **Genetic Polymorphism** Pharmacokinetics differences due to genetic polymorphism have not been studied.
- **Ethnic Origin** The population pharmacokinetic analysis shows that Asians had the strongest association to total irinotecan and SN-38 pharmacokinetics. Compared to Caucasians (N=182, 52%), Asians (N=150, 42%) were observed to have lower concentrations of total irinotecan (C_{avg}: 1.74 mg/L for Asians v. 3.93 mg/L for Caucasians; C_{max} of 27.03 vs. 29.76 mg/L); and higher concentrations of SN-38 (C_{max}: 2.76 [95%CI: 2.62-2.90] ng/mL and 1.78 [95%CI: 1.70-1.87] ng/mL; C_{avg}: 0.87 [95%CI: 0.82-0.92] and 0.72 [95%CI: 0.68-0.77]).

- **Hepatic Insufficiency** The pharmacokinetics of ONIVYDE have not been studied in patients with hepatic impairment. Based on the population pharmacokinetic analysis, higher baseline bilirubin is associated with higher SN-38 concentration following the administration of ONIVYDE. Patients with bilirubin 1.0-2.0 mg/dl (n=19) have approximately 45% higher SN-38 exposure than patients with bilirubin < 1 mg/dl.
  In clinical studies of non-liposomal irinotecan administered on a weekly dosage schedule, patients with modestly elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) had a significantly greater likelihood of experiencing first-cycle Grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL. Use caution in patients with hepatic impairment, particularly in those with bilirubin > 1 mg/dL.
- **Renal Insufficiency** No dedicated pharmacokinetic study has been conducted in patients with renal impairment. In a population pharmacokinetic analysis, mild (CL_{cr} 60 - 89 mL/min) to moderate (CL_{cr} 30 - 59 mL/min) renal impairment had no effect on the exposure of total SN-38 after adjusting for BSA. There was insufficient data in patients with severe renal impairment (CL_{cr} < 30 mL/min) to assess its effect on pharmacokinetics.
  The use of ONIVYDE in patients with significant renal impairment has not been established. In the NAPOLI-1 clinical study no large differences in the safety profile based on mild (CL_{cr} 60 - 89 mL/min) to moderate (CL_{cr} 30 - 59 mL/min) renal impairment were observed. ONIVYDE is not recommended for use in patients with severe renal impairment (CL_{cr} < 30 mL/min).
- **Drug Interactions** No formal pharmacokinetic drug interaction study with ONIVYDE has been conducted. In a population pharmacokinetic analysis, the pharmacokinetics of total irinotecan and total SN-38 were not altered by the co-administration of 5-FU/LV. In vitro studies indicate that irinotecan, SN-38 and another metabolite, aminopentane carboxylic acid (APC), do not inhibit cytochrome P-450 isozymes.

11 STORAGE, STABILITY AND DISPOSAL

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

Room temperature
Diluted suspension should be used immediately, but may be stored at ambient temperature (approximately 25ºC) for up to 4 hours prior to infusion when protected from light.

Refrigeration
Diluted suspension can be stored in the refrigerator at 2ºC to 8ºC (36ºF to 46ºF) for no more than 24 hours prior to use. Allow diluted suspension to come to room temperature (approximately 25ºC) prior to administration. Protect from light. Do NOT freeze.

12 SPECIAL HANDLING INSTRUCTIONS

Do not use any in-line filters. Discard any unused portion.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

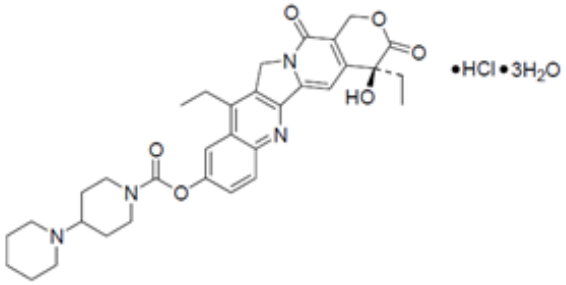
Drug Substance

Proper name: Irinotecan hydrochloride, USP

Chemical name: (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

Molecular formula and molecular mass: $C_{33}H_{38}N_4O_6 \cdot HCL \cdot 3H_2O$ (salt hydrate), 677.19
$C_{33}H_{38}N_4O_6$ (anhydrous free base), 586.68

Structural formula:



Physicochemical properties: Irinotecan hydrochloride trihydrate is a pale yellow to yellow crystalline powder, with a melting range of 250-256 °C.

Irinotecan hydrochloride is hygroscopic. X-ray powder diffraction supports that irinotecan hydrochloride trihydrate exist in one consistent single crystalline form.

The pH of irinotecan hydrochloride trihydrate in a 1% wt/volume solution in water is 3.5-5.0. Irinotecan hydrochloride trihydrate is freely soluble in DMSO and anhydrous acetic acid, and is slightly soluble in ethanol.

Product Characteristics

ONIVYDE (irinotecan liposome for injection) is a topoisomerase inhibitor formulated with irinotecan hydrochloride trihydrate, which is transformed *in situ* to its sucrosofate salt derivative upon its inclusion within the liposomes.

The drug product liposome is a small unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, which encapsulates an aqueous space which contains irinotecan in a gelated or precipitated state, as the sucrose octasulfate salt. The liposome carriers are composed of

1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 6.81 mg/mL; cholesterol, 2.22 mg/mL; N-(carbonyl-methoxypolyethlyene glycol-2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (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; sodium chloride as isotonicity reagent, 8.42 mg/mL. The suspension is buffered at pH 7.25.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Metastatic pancreatic adenocarcinoma

Table 8 - Summary of patient demographics for clinical trials in metastatic pancreatic adenocarcinoma

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
NAPOLI-1	3-arm, randomized, open-label trial	Intravenous administration,	417	63 years (range 31-87 years)	57% men 43% women

Table 9 Efficacy Results of NAPOLI-1 Study

	ONIVYDE + 5-FU/LV (N=117)	**5-FU/LV** (N=119)
Overall Survival*		
Number of Deaths, n (%)	75 (64)	80 (67)
Median Overall Survival (months)	6.1	4.2
(95% CI)	(4.8, 8.9)	(3.3, 5.3)
Hazard Ratio (95% CI)[§]	0.67 (0.49 – 0.92)	
p-value[¶]	0.0122	
Progression-Free Survival[*,†]		
Death or Progression, n (%)	83 (71)	92 (77)
Median Progression-Free Survival (months)	3.1	1.5
(95% CI)	(2.7, 4.2)	(1.4, 1.8)
Hazard Ratio (95% CI) [§]	0.56 (0.41 – 0.75)	
p-value[¶]	0.0001	
Objective Response Rate[†]		
Responder, n	19	1
Rate (%)	16.2	0.8
95% CI of Rate[#]	9.6, 22.9	0.0, 2.5

	ONIVYDE + 5-FU/LV (N=117)	5-FU/LV (N=119)
p-value♠	<0.0001	

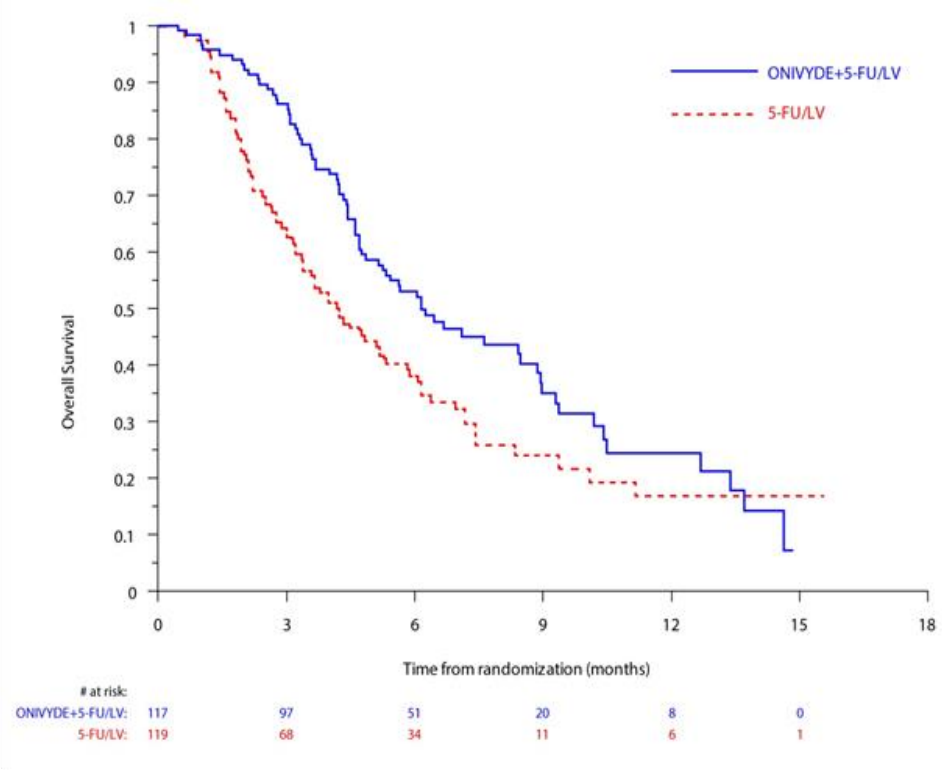
* Median is the Kaplan-Meier estimate of the median survival time
§ Cox model analysis
# Based on Normal approximation
† Per RECIST guidelines, v1.1
¶ Unstratified log-rank test
♠ Fisher's exact test
Abbreviations: 5-FU/LV=5-fluorouracil/leucovorin; CI=confidence interval; PFS=progression free survival; HR=hazard ratio of ONIVYDE+5-FU/LV compared with 5-FU/LV

The efficacy of ONIVYDE was evaluated in the NAPOLI-1 study, a three-arm, randomized, open-label trial in patients with metastatic pancreatic adenocarcinoma with documented disease progression, after gemcitabine or gemcitabine-based therapy. A total of 417 patients were randomised to the ONIVYDE + 5-FU/LV arm (N=117), ONIVYDE monotherapy arm (N=151) and 5-FU/LV arm (N=149). In the intent to treat (all randomised) population, the median age was 63 years (range 31-87 years), 57% were men, 61% were White and 33% were Asian. Mean baseline albumin level was 3.6 g/dL, and baseline Karnofsky Performance Status (KPS) was 90-100 in 55% of patients.

Key eligibility criteria included KPS ≥ 70, serum bilirubin within institution limits of normal, and albumin ≥ 3.0 g/dL. Patients were randomized to receive ONIVYDE+5-FU/LV, ONIVYDE, or 5-FU/LV. Randomization was stratified by ethnicity (White vs. 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/m^2 as an intravenous infusion over 90 minutes, followed by LV 400 mg/m^2 intravenously over 30 minutes, followed by 5-FU 2400 mg/m^2 intravenously over 46 hours, every 2 weeks. The ONIVYDE dose of 70 mg/m^2 is based on irinotecan anhydrous free base (equivalent to 80 mg/m^2 of irinotecan as the hydrochloride trihydrate). Patients randomized to ONIVYDE as a single agent received ONIVYDE 100 mg/m^2 as an intravenous infusion over 90 minutes every 3 weeks. Patients randomized to 5-FU/LV received LV 200 mg/m^2 intravenously over 30 minutes, followed by 5-FU 2000 mg/m^2 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/m^2 ONIVYDE, if given with 5-FU/LV or 70 mg/m^2 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.

Patients received treatment until disease progression or unacceptable toxicity. The primary outcome measure was overall survival (OS). Additional outcome measures included Progression Free Survival (PFS) and Objective Response Rate (ORR). Assessments were conducted at baseline and every 6 weeks thereafter. Results are shown in Table 9. Overall survival is illustrated in Figure 1.

Figure 1. Overall Survival



There was consistency in benefit across the formal stratification factors (performance status, albumin and race).

ONIVYDE monotherapy did not demonstrate a statistically significant benefit in overall survival compared to the 5-FU/LV control arm.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

In single and repeated dose toxicity studies in mice, rats and dogs, the target organs of toxicity were the gastrointestinal tract and the hematologic system. The severity of effects was dose-related and reversible. The no-observed-adverse-effect level (NOAEL) in rats and dogs following 90 min intravenous infusion of ONIVYDE once every 3 weeks for 18 weeks was at least 156 mg/m^2. No findings indicative of CNS related toxicity were observed in the repeated dose toxicity studies in rats.

In safety pharmacology studies in dogs, ONIVYDE had no effect on cardiovascular, hemodynamic, electrocardiographic, or respiratory parameters at doses of irinotecan (as anhydrous free base) up to 18 mg/kg (364 mg/m^2).

Carcinogenicity

Studies to evaluate the mutagenesis and carcinogenicity of ONIVYDE were not conducted. Non-liposomal irinotecan has been studied in experimental models and was shown to be clastogenic both in vitro (chromosome aberrations in Chinese hamster ovary cells) and in vivo (micronucleus test in mice). In rats, there was a significant linear trend between non-liposomal irinotecan (as anhydrous free base) dosage (1.7 and 22 mg/kg, IV, once weekly for 13 weeks followed by a 91 week treatment-free period) and the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas. Neither non-liposomal irinotecan nor its active metabolite, SN-38, were mutagenic in the in vitro Ames test.

Reproductive and Developmental Toxicology

No fertility studies were performed with ONIVYDE. However, in dogs receiving ONIVYDE at doses equal to or greater than 18 mg/kg (364 mg/m^2) once every 3 weeks for 6 cycles, findings included minimal to moderate effects on various cell types and organs of the reproductive tract in males and females, similar to effects seen with non-liposomal irinotecan. No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of non-liposomal irinotecan in doses of up to 5 mg/kg/day (as anhydrous free base) to rats and rabbits; however, atrophy of male reproductive organs was observed after multiple daily non-liposomal irinotecan doses both in rodents at 17 mg/kg and in dogs at 0.3 mg/kg (as anhydrous free base).

Special Toxicology

There are no animal data on teratogenic/embryotoxic effects for ONIVYDE. Intravenous administration of irinotecan 5 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 produced an irinotecan C_{max} and AUC of about 2 and 0.2 times, respectively, the corresponding values in patients administered 108 mg/m^2 (as anhydrous free base). In rabbits, the embryotoxic dose was about one-half the recommended human weekly starting dose on a mg/m^2 basis. Non-liposomal irinotecan was teratogenic in rats at doses greater than 1 mg/kg/day and in rabbits at 5 mg/kg/day (as anhydrous free base). In separate studies in rats, this dose produced an irinotecan C_{max} and AUC about 2/3 and 1/40th, respectively, of the corresponding values in patients administered 108 mg/m^2 (as anhydrous free base). In rabbits, the teratogenic dose was about one-half the recommended human weekly starting dose on a mg/m^2 basis. Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Non-liposomal irinotecan administered to rat dams for the period following organogenesis through weaning at doses of 5 mg/kg/day (as anhydrous free base) caused decreased learning ability and decreased female body weights in the offspring.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]ONIVYDE®
Irinotecan Liposome for Injection

Read this carefully before you start taking **ONIVYDE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ONIVYDE**.

Serious Warnings and Precautions

Your ONIVYDE administration must be supervised by a doctor with specific experience in the use of cancer chemotherapy medicines.

Do **NOT** substitute ONIVYDE for other medicines that contain irinotecan. ONIVYDE is not the same as other medicines containing irinotecan. Ask your healthcare professional if you have any questions.

ONIVYDE can cause serious side effects which include:

- **Diarrhea:** This can happen during or right after you receive ONIVYDE (early onset), or more than 24 hours after you receive it (late onset). Late onset diarrhea can be fatal. If you have any signs of diarrhea (e.g., loose or watery, and frequent stools), tell your healthcare professional right away. Drink a lot of clear liquids (e.g., water, apple juice, broth, sports drinks, or non-fizzy soft drinks) to prevent dehydration (loss of body fluid). In some cases, your healthcare professional may need to reduce and/or stop your dose of ONIVYDE. Diarrhea treatment (e.g., with a medicine that contains loperamide) may also be provided by your healthcare professional for up to 48 hours.

- **Neutropenia** (decreased white blood cells): This can increase your risk of a potentially serious and life-threatening infection. Your healthcare professional will monitor your white blood cell count and will adjust your dose as necessary. The risk of neutropenia is higher if you:
  - are of an Asian descent,
  - have certain liver problems, and
  - have had genetic testing done and been told that you are homozygous for the UGT1A1*28 allele (UGT1A1 7 / 7 genotype).

See the **Serious side effects and what to do about them** table below for more information on these and other serious side effects.

What is ONIVYDE used for?

ONIVYDE is used to treat adults (18 years of age and older) with metastatic pancreatic cancer (a type of cancer that starts in the pancreas and has already spread elsewhere in the

body).

It is used:

- in patients who had their cancer progress after receiving another medicine called gemcitabine, and
- in combination with other cancer medicines called 5-fluorouracil (5-FU) and leucovorin (LV).

How does ONIVYDE work?

ONIVYDE belongs to a group of medicines called “topoisomerase inhibitors”. It is used in combination with other medicines to treat cancer. It blocks an enzyme that is involved in the division of cancer cells. This prevents these cells from multiplying and growing and they eventually die.

The medicine in ONIVYDE is held within small fatty particles called liposomes. The liposomes build up in the tumor and release the medicine slowly over time, which allows it to act for a longer period.

What are the ingredients in ONIVYDE?

Medicinal ingredient: Irinotecan (as sucrose octasulfate salt).

Non-medicinal ingredients: 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid (HEPES), cholesterol, N-(carbonyl-methoxypolyethylene glycol-2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-2000-DSPE), sodium chloride, sucrose octasulfate, and water for injection.

ONVIYDE comes in the following dosage forms:
Suspension: 4.3 mg/mL of irinotecan (as sucrose octasulfate salt).

Do not use ONIVYDE if:

- you had a severe allergic reaction to any medicine containing irinotecan in the past.
- you are allergic to irinotecan or any of the ingredients in ONIVYDE.
- you are breast-feeding or planning to breast-feed.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ONIVYDE. Talk about any health conditions or problems you may have, including if you:

- have previously been given any medicine that contains irinotecan in any form as it may act differently than ONIVYDE. It is unknown if ONIVYDE provides a benefit in people who have previously received other medicines containing irinotecan.
- have had genetic testing done and been told that you are homozygous for the UGT1A1*28 allele (UGT1A1 7 / 7 genotype). This could increase your risk of getting neutropenia (decreased white blood cells).
- have or have had liver problems.
- have or have had kidney problems.
- have or have had bone marrow problems.

- have interstitial lung disease (ILD; scaring of the lung tissue) or
- are at a higher risk of developing ILD. This includes if you:
    - have or have had lung problems;
    - are taking pneumotoxic medicines that have a toxic effect on the lungs;
    - are taking medicines to increase your white blood cell count called colony stimulating factors;
    - have ever received radiation therapy.
- have recently received a vaccine or are going to receive a vaccine. Your response to the vaccine may be reduced.
- are underweight or have been told that you have a low body mass index (less than 18.5 kg / m^2).
- have had a surgery on your pancreas known as a Whipple procedure.
- have a bowel obstruction (the flow of food and liquid in the intestines is blocked).
- are pregnant or planning to become pregnant.
- are at a higher risk of developing blood clots.
- are 75 years of age or older.

Other warnings you should know about:
ONIVYDE can cause the following serious side effects:

- **Allergic reactions:** Tell your healthcare professional right away if you experience any signs of an allergic reaction. This can include:
    - swelling under the skin (angioedema),
    - sudden shortness of breath or difficulty breathing,
    - flushing,
    - nausea,
    - headache,
    - skin rash or hives (itchy rash with swollen red bumps on the skin that appear suddenly),
    - itching,
    - swelling around the eyes, and
    - tightness in the chest or throat during the infusion or shortly after it.

Severe allergic reactions may be life threatening. The infusion may need to be stopped and you may need to be treated or observed for the side effects.

- **Blood clots:** Taking ONIVYDE can cause blood clots (thrombosis). These clots can be in the lung (pulmonary embolism), the veins (venous thrombosis), or the arteries (arterial thromboembolism). Contact your healthcare professional right away if you develop any signs or symptoms of a blood clot including:
    - swelling, pain, muscle spasms, tenderness or discolouration in the leg or arms;
    - chest pain, difficulty breathing, shortness of breath, coughing up blood;
    - slurred speech, face drooping to one side;
    - weakness, dizziness, headache.

See the **Serious side effects and what to do about them** table below for more information on these and other serious side effects.

Pregnancy, breast-feeding, and fertility:
Women:

- You should not receive ONIVYDE if you are pregnant as it may harm your baby.

You must tell your healthcare professional if you are or think you may be pregnant. Your healthcare professional may give you a pregnancy test before and during your treatment with ONIVYDE. Ask your healthcare professional for advice if you are planning to have a baby.

- During your ONIVYDE treatment and for 7 months after you receive your last dose, you should not become pregnant. Use an effective birth control method during this time. Talk to your healthcare professional for advice on effective methods of birth control.
- Do NOT take ONIVYDE if you are breast-feeding or planning to breast-feed. In addition, you should not breast-feed until one month after your last dose of ONIVYDE. Ask your healthcare professional if you are unsure.
- Prior to taking this medicine talk with your healthcare professional about the possible risks with this medicine and the options that may preserve your ability to have children.

Men:

- Use condoms if you have sex during your treatment and for at least four months after your last dose.

Driving and using machines:

ONIVYDE may affect your ability to drive or use machines. Before doing tasks which require special attention like driving, wait until you are feeling well again.

Testing and monitoring:

- ONIVYDE may cause abnormal blood test results.
- Your healthcare professional will monitor your health before, during, and after your treatment with ONIVYDE. This may include doing blood tests, monitoring signs of infections, and monitoring your lung function. Your healthcare professional may adjust your dose of ONIVYDE, delay treatment, or stop your treatment based on the results of these tests.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ONIVYDE:

- antibiotics, medicines used to treat bacterial infections (e.g., rifampin, rifabutin, azithromycin, clarithromycin, erythromycin, ciprofloxacin, and norfloxacin).
- antiepileptics, medicines used to treat and prevent seizures (e.g., carbamazepine, phenytoin, and phenobarbital).
- antifungals, medicines used to treat fungal infections (e.g., ketoconazole, fluconazole, itraconazole, and voriconazole)
- antiretrovirals, medicines used to treat HIV/AIDS (e.g., indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and atazanavir)
- calcium channel blockers, medicines used to treat high blood pressure and chest pain (e.g., diltiazem, verapamil, and nifedipine).
- cimetidine, a medicine used to treat stomach and intestine ulcers.
- gemfibrozil, a medicine used to treat high fat levels in the blood

- glucocorticoids, steroid medicines used to reduce inflammation.
- grapefruit juice. Do NOT drink grapefruit juice while receiving ONIVYDE.
- nefazodone, a medicine used to treat depression.
- St. John's Wort, a herbal medicine.
- telaprevir, a medicine used to treat Hepatitis C.

How to take ONIVYDE:

- ONIVYDE will be prepared and given to you by a healthcare professional with experience in the use of cancer chemotherapy medicines.
- You will receive ONIVYDE into your veins (i.e., "intravenously" or "IV) over a period of 90 minutes. Your healthcare professional will then give you two other cancer medicines, leucovorin (LV) and 5-fluorouracil (5-FU).
- Follow all instructions given to you by your healthcare professional.
- Your healthcare professional may also give you other medicines to prevent nausea, vomiting, diarrhea, or allergic reactions.

Usual dose:

Your healthcare professional will decide how much and how long you should be treated with ONIVYDE. Your dose may depend on your condition, weight, age, if you are taking other medicines, and how you respond to ONIVYDE. Your dose will be repeated every two weeks.

Overdose:

If you think you, or a person you are caring for, have taken too much ONIVYDE, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

What are possible side effects from using ONIVYDE?

These are not all the possible side effects you may have when taking ONIVYDE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects of ONIVYDE may include:

- hair loss

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Anemia (decreased red blood cells): dizziness, feeling tired and weak, loss of energy, or shortness of breath.		**X**	
Diarrhea (loose or watery and frequent stools)		**X**	
Feeling tired	**X**		

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Fever (increase in body temperature)		**X**	
Hypokalemia (low level of potassium in the blood): generally feeling unwell, irregular heartbeat, muscle cramps, paralysis, twitches or weakness.		**X**	
Loss of appetite	**X**		
Nausea	**X**		
Neutropenia (decreased white blood cells): aches, feeling tired, fever, flu-like symptoms, or infections.		**X**	
Stomatitis (mouth sores and swelling): burning sensation and pain in the mouth, difficulty eating, swelling or sores in the mouth.		**X**	
Thrombocytopenia (decreased platelets in the blood); bleeding, bruising, fatigue, or weakness.		**X**	
Vomiting	**X**		
Weight loss	**X**		
COMMON			
Acute kidney failure (fast decline in proper functioning of the kidney): confusion, feeling weak, nausea, loss of appetite, personality changes, or vomiting.		**X**	
Dehydration (loss of body fluid): confusion, dizziness, dry mouth, fainting, feeling thirsty, headache, irritability, or urinating less than normal.		**X**	
Diarrhea followed by a stuffy and runny nose, sneezing, post-nasal drip, increased salivation, flushing, slowing of heartbeat, constriction of pupils, watery eyes and production of tears, sweating, or abdominal cramping.		**X**	
Gastroenteritis (inflammation of the stomach and intestines): abdominal pain, diarrhea, nausea, or vomiting.		**X**	
Hypomagnesemia (low level of magnesium in the blood): feeling tired, loss of appetite, muscle spasms, shaking, vomiting, or weakness.		**X**	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Infection or allergic reaction at injection site: pain, redness or swelling.		**X**	
Pneumonia (infection of the lungs): cough, difficult or painful breathing, fever, shortness of breath, or wheezing.		**X**	
Sepsis and septic shock (life-threatening complication of an infection): chills, high or very low body temperature, little or no urine, low blood pressure, palpitations, rapid breathing, or rapid heartbeat.		**X**	
Thrombotic events (blood clot in a blood vessel): pain, swelling or redness in one part of the body.			**X**
UNCOMMON			
Arterial thromboembolism and venous thrombosis (blood clots in arteries and veins): swelling, pain, muscle spasms, tenderness or discolouration in the legs or arms, chest pain, shortness of breath, slurred speech, face drooping to one side, weakness, dizziness, or headache			**X**
Heart attack (loss of blood supply to the heart): sudden chest pain, pressure or discomfort, feeling faint, feeling anxious, shortness of breath, irregular heartbeat, nausea, or sudden heavy sweating.			**X**
Pulmonary embolism (blood clot in the lungs): coughing up of blood, difficulty breathing, sharp pain in the chest, or sudden shortness of breath.			**X**
Stroke (loss of blood to the brain): confusion, feeling dizzy, numbness or weakness in an arm or leg or the face, loss of coordination, muscle weakness, trouble seeing or speaking, or sudden severe headache.			**X**
UNKNOWN FREQUENCY			

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Allergic reaction: sudden shortness of breath, flushing, nausea, headache, skin rash or hives (itchy rash with swollen red bumps on the skin that appear suddenly), itching, swelling around the eyes, and tightness in the chest or throat during the infusion or shortly after it, or swelling under the skin.			**X**
Interstitial lung disease, including pneumonitis (inflammation of the lungs): new or progressive shortness of breath, tiredness, cough, or fever.			**X**

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Your healthcare professional will store the unopened ONIVYDE vials for you in a refrigerator between 2ºC to 8ºC. ONIVYDE will be protected from light and freezing.

ONIVYDE is a cytotoxic drug. All applicable special handing and disposable procedures must be followed.

Keep out of reach and sight of children.

If you want more information about ONIVYDE:

- Talk to your healthcare professional.
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website

(https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html), the manufacturer's website www.ipsen.ca or by calling 1-855-215-2288.

This leaflet was prepared by Ipsen Biopharmaceuticals Canada Inc.

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