onivyde®
(irinotecan liposome injection)

Welcome to the ONIVYDE® patient brochure

Please see Important Safety Information on pages 28-31, and accompanying full Prescribing Information, including Boxed Warnings for ONIVYDE®.

WHAT IS ONIVYDE USED FOR?

ONIVYDE (irinotecan liposome injection) is a prescription medicine used to treat pancreatic cancer which has spread to other parts of the body. ONIVYDE can be used in patients who have already received gemcitabine treatment for their pancreatic cancer. ONIVYDE is given in combination with 2 other medicines, fluorouracil (also known as 5-FU) and leucovorin (which is often abbreviated as LV), and is not given alone.

SELECTED IMPORTANT SAFETY INFORMATION

ONIVYDE can cause problems that can sometimes become serious or life threatening and can lead to death. Serious side effects may include fever and infection associated with a low white blood cell count (neutropenic fever, neutropenic sepsis); diarrhea; lung problems (interstitial lung disease, a group of diseases which cause inflammation of the lung tissues leading to scarring); and reactions during administration of ONIVYDE (including anaphylactic reactions).

Before you receive ONIVYDE, your healthcare provider will give you medications to decrease the potential for allergic reactions to infusion of ONIVYDE. You will also receive anti-nausea medicine to decrease nausea and vomiting, and, possibly, a medicine to decrease immediate diarrhea, called an anti-cholinergic.

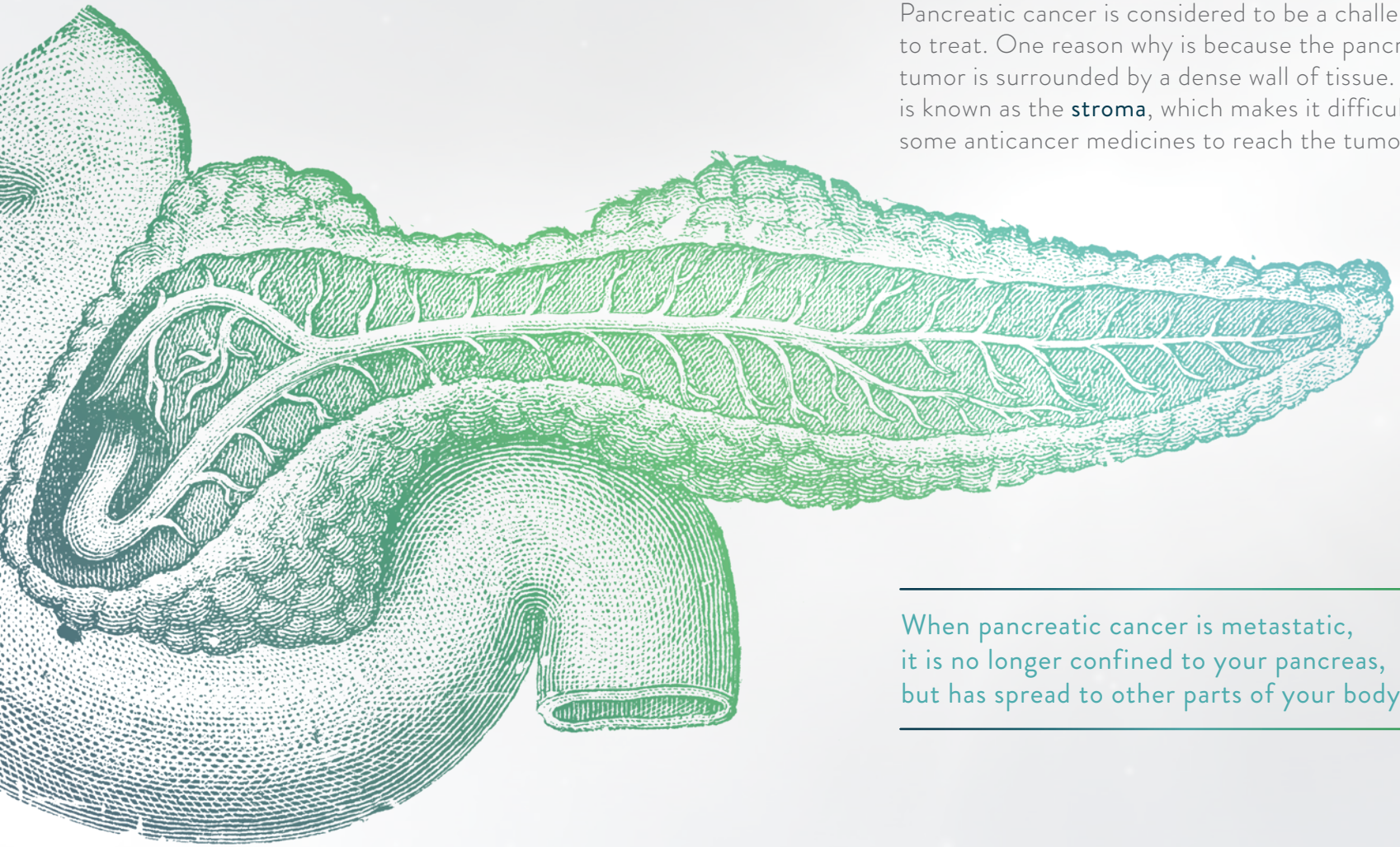
Please see additional Important Safety Information on pages 28-31, and accompanying full Prescribing Information, including Boxed Warnings for ONIVYDE®.

STAY IN THE FIGHT

This brochure offers you useful information about ONIVYDE® and includes pancreatic cancer resources that may be helpful during your treatment.

A challenging type of cancer.

Pancreatic cancer is considered to be a challenge to treat. One reason why is because the pancreatic tumor is surrounded by a dense wall of tissue. This is known as the **stroma**, which makes it difficult for some anticancer medicines to reach the tumor.

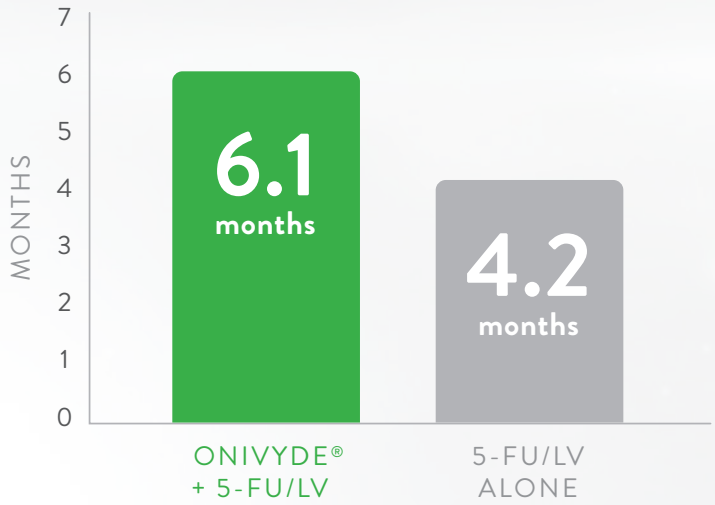


When pancreatic cancer is metastatic, it is no longer confined to your pancreas, but has spread to other parts of your body.

Proven to help you fight pancreatic cancer.

After disease progression following gemcitabine-based therapy, ONIVYDE® (irinotecan liposome injection) is proven to help people with **metastatic** pancreatic cancer live longer, when given in combination with 2 other medicines, **fluorouracil** (5-FU) and **leucovorin** (LV).

Overall Survival Data*



**Data from NAPOLI-1, a global, randomized, phase 3 clinical trial.*

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The study showed that ONIVYDE® + 5-FU/LV:

- Helped people live longer (**6.1 months vs 4.2 months** for 5-FU/LV alone)—which is known as **median** overall survival
- Extended the time during which the patient lived without the disease getting worse (**3.1 months vs 1.5 months** for 5-FU/LV alone)—which is known as median progression-free survival

The study's results led to the FDA approval of ONIVYDE® + 5-FU/LV as the first treatment for metastatic pancreatic cancer after chemotherapy using gemcitabine.

SELECTED IMPORTANT SAFETY INFORMATION

When should ONIVYDE not be given?
You should not receive ONIVYDE if:

- you have had a **severe allergic reaction to ONIVYDE or irinotecan HCl**,
- your **white blood cell count is low** (neutrophil white blood cell count below the level of 1,500 cells/mm^3),
- you have a **fever and your neutrophil white blood cell count is low** (also called neutropenic fever), or
- you have a **problem in your bowel** that prevents food, fluids or gas from moving through your intestines.

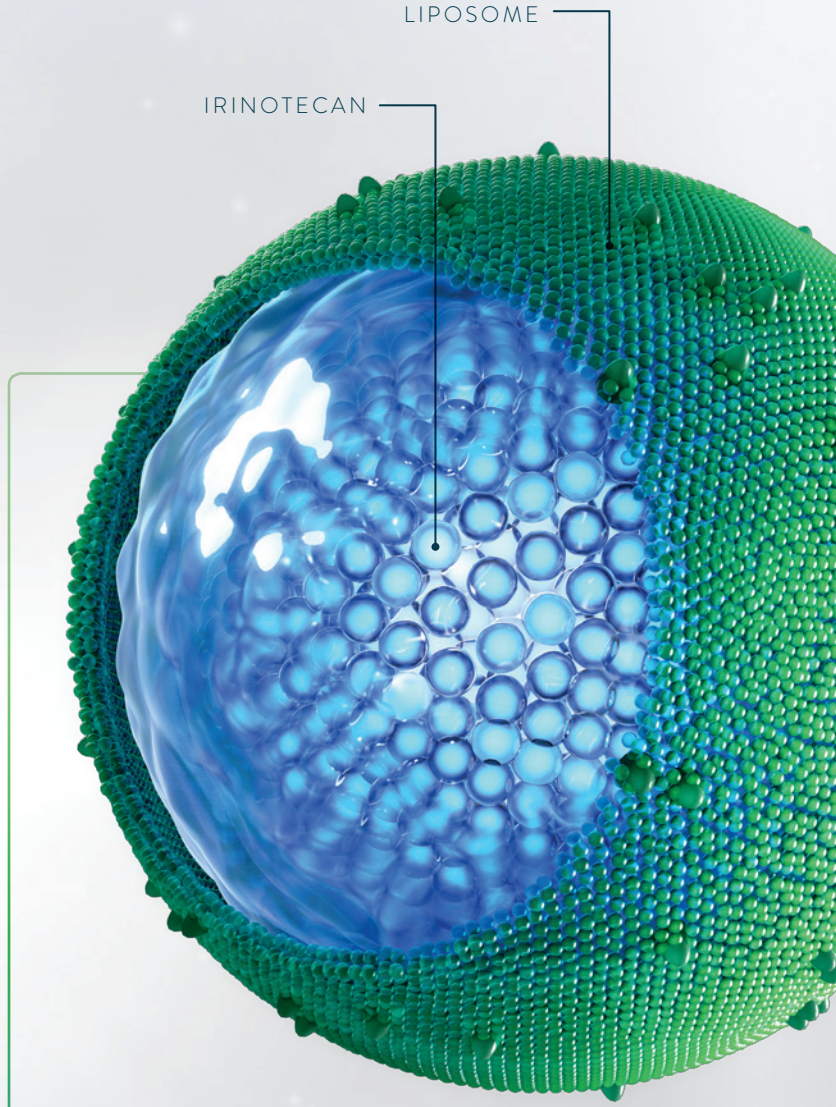
How ONIVYDE® (irinotecan liposome injection) works.

ONIVYDE® has a unique design that helps it fight **metastatic** pancreatic cancer. A protective shell, called a **liposome**, surrounds an anticancer drug, called **irinotecan**. The liposome helps ONIVYDE® stay in circulation in your body.

SELECTED IMPORTANT SAFETY INFORMATION

Serious side effects may occur while taking ONIVYDE. Call or see your healthcare provider right away if you develop any of the following or if these get worse. Serious side effects may include infections (particularly if your white blood cells are low), diarrhea, lung problems (interstitial lung disease), and allergic reaction (hypersensitivity).

Please see additional Important Safety Information on pages 28-31, and accompanying full Prescribing Information, including Boxed Warnings for ONIVYDE®.



ONIVYDE® was designed to help irinotecan get through the dense stroma of the pancreatic tumor.

Things to know about side effects.

During your treatment with ONIVYDE® (irinotecan liposome injection) + 5-FU/LV, you may get certain side effects that can be serious.

The most common side effects include diarrhea, tiredness/weakness, vomiting, nausea, decreased appetite, mouth sores, and fever. The most common blood count change seen is a reduction in the number of white blood cells, which are important for fighting infections.

Serious side effects may include infections (particularly if your white blood cells are low), diarrhea, lung problems (interstitial lung disease), and allergic reaction (hypersensitivity).

With the help of your doctor and treatment team, there may be ways to help manage some of these side effects.

If you get certain serious side effects during treatment with ONIVYDE® + 5-FU/LV, your doctor may choose to delay or withhold your dose, or stop your treatment.

It's not unusual to have a dose delayed or withheld. More than half of the patients in the clinical study that led to the approval of ONIVYDE® had a dose delayed or withheld.

How ONIVYDE® is given to you.

ONIVYDE® is given to you in combination with 2 other medicines, **fluorouracil** (5-FU) and **leucovorin** (LV). You are given ONIVYDE® + 5-FU/LV by **intravenous infusion** (IV), which is when medicine is injected into your vein. Your treatment will be given to you by a healthcare professional who is trained to administer **chemotherapy**.

Your doctor will determine the dose of ONIVYDE® that is best for you.

You will always be given ONIVYDE® in combination with 5-FU and LV.

Please see additional Important Safety Information on pages 28-31, and accompanying full Prescribing Information, including Boxed Warnings for ONIVYDE®.

Given in a treatment cycle.

ONIVYDE® (irinotecan liposome injection) + 5-FU/LV is given to you in 3 steps. This is known as a treatment cycle.

Each treatment cycle lasts for 2 weeks, which includes the time when you won't be given any **chemotherapy**.

You'll be given ONIVYDE® and **leucovorin** (LV) by a healthcare professional in an infusion center. You'll start **fluorouracil** (5-FU) in an infusion center, and may continue it at home using a portable infusion pump.

Please see additional Important Safety Information on pages 28-31, and accompanying full Prescribing Information, including Boxed Warnings for ONIVYDE®.

Treatment cycle at a glance

Step 1 ONIVYDE®	Given for **90 min**	In the infusion center
Step 2 Leucovorin (LV)	Given for **30 min**	In the infusion center
Step 3 Fluorouracil (5-FU)	Given for **46 hrs**	In the infusion center & at home

No further **chemotherapy** until the next treatment cycle begins

SELECTED IMPORTANT SAFETY INFORMATION

- The most frequent side effects resulting in **discontinuation** of ONIVYDE were diarrhea, vomiting, and infection caused by low white blood cells (neutropenic sepsis).
- The most frequent side effects requiring **dose reductions** of ONIVYDE were neutropenia, diarrhea, nausea, and low red blood cell count (anemia).
- The most frequent side effects requiring **dose interruptions or delays** of ONIVYDE were neutropenia, diarrhea, fatigue, vomiting, and low platelet counts called thrombocytopenia (platelets are important for clotting to stop bleeding).

Considerations with your treatment.

Before you receive ONIVYDE® (irinotecan liposome injection), your doctor may give you medicine to prevent or reduce nausea and vomiting. Your doctor may also give you medicine to prevent or reduce diarrhea.

Also, if you have certain medical conditions, you won't be given ONIVYDE®. These include:

- A severe allergic reaction to ONIVYDE® or **irinotecan**, its anticancer medicine
- A low **white blood cell count**
- A low white blood cell count with fever (called neutropenic fever)
- An obstruction in your bowel

During your therapy, your doctor will test your blood from time to time. This is to check your white blood cell count, specifically your absolute neutrophil count (also known as ANC), to make sure you have enough of certain white blood cells (such as **lymphocytes** and **neutrophils**) that fight infection.

SELECTED IMPORTANT SAFETY INFORMATION

Tell your healthcare provider about all the medicines you take, including:

- prescriptions
- over-the-counter medicines
- vitamins
- herbal supplements

To avoid possible drug interactions with your therapy, be sure to tell your doctor if you're taking any prescription or over-the-counter medicines, vitamins, or herbal supplements.

Please see additional Important Safety Information on pages 28-31, and accompanying full Prescribing Information, including Boxed Warnings for ONIVYDE®.

About serious side effects.

During your treatment with ONIVYDE® (irinotecan liposome injection) + 5-FU/LV, you may get certain side effects that are serious, and which could be fatal, such as diarrhea, an infection, a lung problem, or a severe allergic reaction.

IMPORTANT! **If you feel you have *any side effect* from treatment with ONIVYDE® + 5 FU/LV, get in touch with a healthcare professional *right away*.**

SELECTED IMPORTANT SAFETY INFORMATION

Pregnancy and Nursing

If you are a female, tell your healthcare provider if you are pregnant or plan to become pregnant. ONIVYDE can harm your unborn baby. Females who are able to become pregnant should use an effective method of birth control during and for at least 1 month after the last dose of ONIVYDE. Talk to your healthcare provider about birth control methods that you can use during this time.

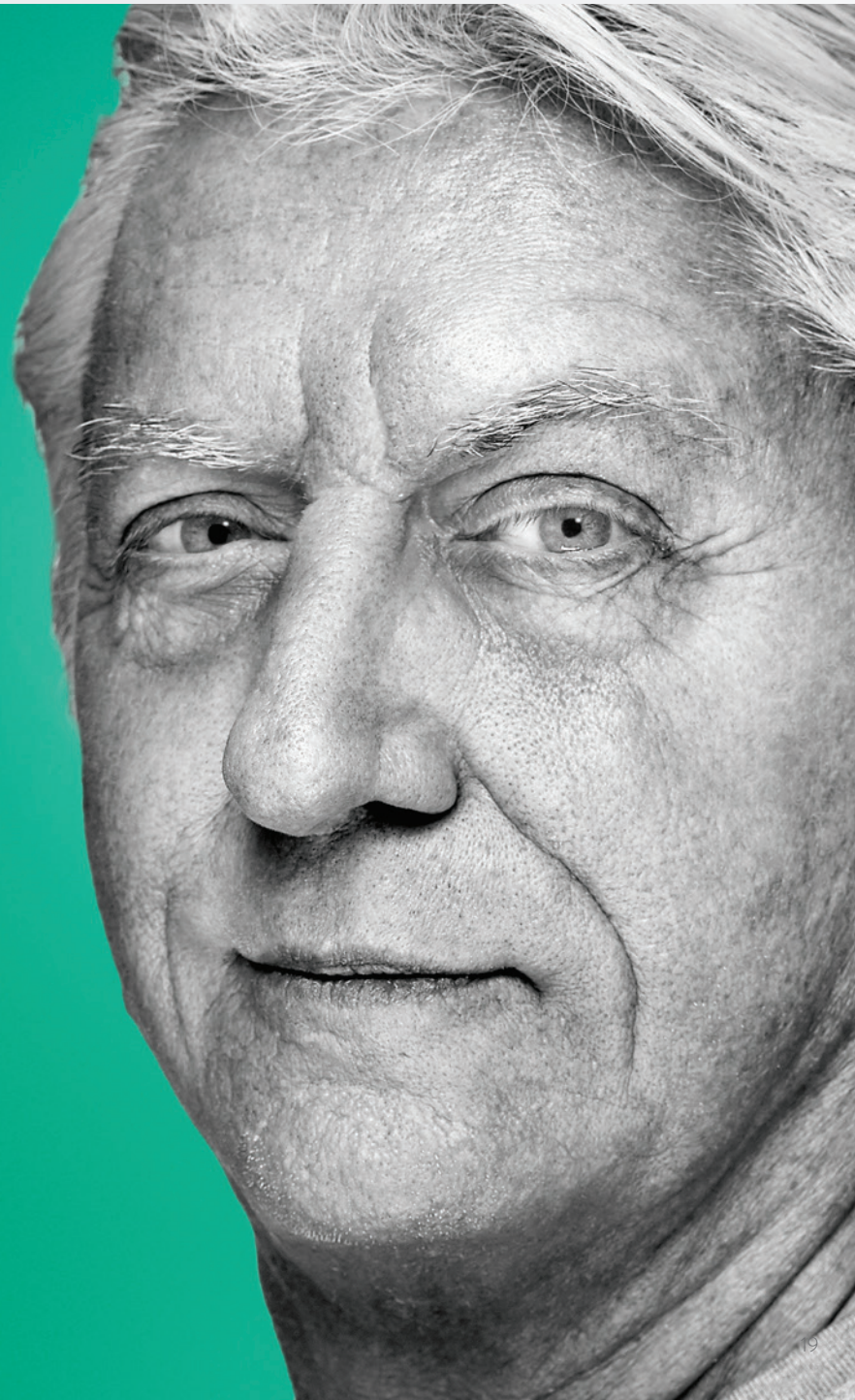
If you are a man, you should not father a child during your treatment with ONIVYDE. ONIVYDE can harm the unborn baby of your partner. You should use an effective method of birth control during and for at least 4 months after the last dose of ONIVYDE.

Please see additional Important Safety Information on pages 28-31, and accompanying full Prescribing Information, including Boxed Warnings for ONIVYDE®.

Serious and potentially fatal side effects of treatment with ONIVYDE® + 5-FU/LV

Serious side effect	Common symptoms	What you should do
Diarrhea can start early (within 24 hours after being given ONIVYDE®) or late (over 24 hours after being given ONIVYDE®).	Diarrhea that won't stop, discolored stools (black, green, or bloody), symptoms of dehydration (feeling dizzy, lightheaded, or faint).	**Contact your doctor or treatment team.** Your doctor may give you antidiarrhea medicine, such as loperamide or atropine, or reduce your dose or stop your treatment.
Serious infections can occur during your treatment with ONIVYDE®, especially if your **white blood cell count** is low.	Fever, chills, feeling dizzy, feeling short of breath.	**Contact your doctor or treatment team.** Your doctor will monitor your white blood cell count from time to time during your treatment, to be sure you don't get **neutropenia**.
Serious lung problems (interstitial lung disease) can occur during your treatment with ONIVYDE®.	New coughing, difficulty breathing, fever.	**Contact your doctor or treatment team.**
A severe allergic reaction (hypersensitivity) can occur during your treatment with ONIVYDE®.	Tightness in your chest, feeling short of breath, feeling dizzy or faint, wheezing, swelling of your face, eyelids, or lips—either while being given or within 24 hours after being given ONIVYDE®.	**SEEK MEDICAL ATTENTION IMMEDIATELY.**

Resources.



Managing diarrhea during treatment.

Diarrhea is a common—and sometimes serious—side effect of **chemotherapy**. If you experience diarrhea during your treatment, your doctor may give you antidiarrhea medicine, such as loperamide or atropine. If you experience diarrhea that is serious, your doctor will withhold your treatment, and may continue it at a lower dose if your diarrhea gets better.

IMPORTANT! If you have *any symptoms* of diarrhea, you should contact your doctor and treatment team *right away*.

If you have diarrhea, it's a good idea to **track the time, duration, and consistency of your stools**, so you can give these details to your doctor and treatment team. To do so, you can **use the side effects log that's included with this brochure.** It's also a good idea to track how much fluid you're taking in, since diarrhea can cause dehydration.

In addition to your doctor's advice, there are some things you can do that may help manage diarrhea:

Eat

- Smaller amounts of food, and more often (about 6-8 small servings per day)
- Foods containing soluble fiber such as high-pectin fruits (bananas, strawberries, peeled apples) and certain cooked vegetables (carrots)
- Food rich in potassium (bananas, oranges, peeled potatoes)
- Foods low in fat

Drink

- Plenty of cool (but not hot), clear liquids (such as water or soup) that can help you rehydrate. It's important to stay hydrated, to avoid losing excess fluid from your body
- 1 cup of liquid for each stool that appears. If you're feeling nauseated and can't keep water down, try sucking on ice chips. If you're not drinking enough water or notice any symptoms of dehydration, be sure to alert your doctor and treatment team right away

Avoid

- Foods with insoluble fiber such as whole grain bread and cereal, fruits with peels, raw nuts, and uncooked vegetables
- Foods that are greasy, fatty, fried, or spicy (such as fast foods, some meats and cheeses, sour cream, and whole milk)
- Coffee, tea, or alcohol
- Dairy products (if you are lactose intolerant)

Caring for yourself with diet and nutrition.

If you have pancreatic cancer, it can be especially important to maintain a good weight and energy level, which can be vital to your overall sense of well-being.

Pancreatic cancer can hinder you from getting vital nutrients from foods you eat (called malabsorption), because your pancreas isn't producing enough of the enzymes that help you digest. You can also lose your appetite, since you just don't feel like eating if you don't feel well. But it's important to keep eating—even when you don't feel like it—so you don't lose muscle mass, body weight, and strength.

Certain dieticians specialize in helping people with cancer. They have the credential **CSO (Certified Specialist in Oncology)**. It's a good idea to ask your doctor and treatment team about getting in touch with one. Also, keep in mind that for managing side effects, your doctor and treatment team are your best sources of advice.

Your best course of action is to take steps to get enough calories, protein, vitamins, and minerals every day. Here are some tips:

- Eat small meals slowly and frequently throughout the day
- Make sure each meal has enough protein
- Eat at least 2-3 cups of vegetables a day
- Drink enough fluids (such as water, pure juice, or electrolyte drinks), and at least an hour before and after eating
- Avoid alcoholic drinks
- Avoid drinks and foods with caffeine (such as soda, coffee, tea, or chocolate)
- Avoid sweets or foods high in fat

IPSEN CARES® support program.

IPSEN CARES® acts as a single point of contact between you, your insurance company, and your doctor's office. The program features a wide range of services to support your treatment with ONIVYDE® (irinotecan liposome injection).

- Helps you navigate the insurance process to determine out-of-pocket costs
- Helps with copay assistance*
- Provides medicine at no cost through the Assistance Program*
- Assists with finding an in-network specialty pharmacy, if requested by the provider
- Helps minimize treatment delays or interruptions caused by coverage and payment matters

To learn more, visit IPSENCARES.com, or call (866) 435-5677 between the hours of 8 AM and 8 PM EST, Monday through Friday.

**For eligible patients. See the full Terms and Conditions at IPSENCARES.com*

Please see additional Important Safety Information on pages 28-31, and accompanying full Prescribing Information, including Boxed Warnings for ONIVYDE®.

Support groups for pancreatic cancer.

Coping with the physical and emotional impacts of cancer can be difficult. Fortunately, you are *not alone*. The following is a list of helpful organizations for people with pancreatic cancer and their caregivers.

Pancreatic Cancer Action Network®

(877) 272-6226
pancan.org

The Pancreatic Cancer Action Network® (PanCAN®) provides no-cost personalized education and support for pancreatic cancer patients and their caregivers, by email and by phone.

National Comprehensive Cancer Network®

(215) 690-0300
nccn.org

The National Comprehensive Cancer Network® (NCCN®) is dedicated to improving the quality of cancer care, so patients can lead better lives. Treatment with liposomal irinotecan (ONIVYDE®) + 5-FU/LV is a recommended option by the NCCN for certain people with metastatic pancreatic cancer.

The Lustgarten Foundation's "Let's Win! Pancreatic Cancer" Initiative

letswinpc.org

The Lustgarten Foundation supports pancreatic cancer research. Its patient initiative, "Let's Win! Pancreatic Cancer", offers patient videos, management tips, and research news, along with other helpful resources.

Glossary of common terms.

The following is a list of common terms relating to pancreatic cancer and your treatment with ONIVYDE® (irinotecan liposome injection) + 5-FU/LV.

Chemotherapy *(kee-moh-THEH-ra-pee)*
Medicines or drugs used to treat cancer. Commonly referred to as "chemo."

Fluorouracil *(floor-oh-YOOR-a-sil)*
A chemotherapy drug used to treat certain types of cancer. Also known as "5-FU."

Gemcitabine *(gem-SITE-a-bean)*
A chemotherapy drug used to treat certain types of cancer.

Intravenous *(in-truh-VEE-nuss)* **infusion**
A method of delivering fluids and medicine using a needle or thin tube (called a catheter) inserted into a vein. Often referred to as "IV."

Irinotecan *(ear-ee-no-TEE-can)*
A chemotherapy drug used to treat certain types of cancer.

Leucovorin *(loo-koh-VOOR-in)*
A drug (also called "folinic acid," and derived from folic acid) used to treat certain types of cancer, as well as certain types of anemia. Also known as "LV."

Liposome *(LIPE-oh-sohm)*
A formulation that helps to deliver microscopic substances (such as anticancer drugs) to cells in the body.

Lymphocytes *(LIM-foh-sites)*
Cells that originate from stem cells, making up about 20-30 percent of the white blood cells found in normal human blood.

Median
A number that's the number in the middle of a set of numbers that are going up or down in value. For example, the median of the set of numbers 2, 3, 5, 7, 9, 13, 17 is the number 7.

Metastatic *(meh-tuh-STA-tik)*
Cancer that has spread from where it first started (the primary site) to other organs or structures in the body.

Neutropenia *(noo-troh-PEE-nee-uh)*
A decrease in the number of white blood cells (neutrophils) that respond quickly to an infection. Having neutropenia increases a person's risk of getting an infection.

Neutrophils *(NOO-troh-fills)*
White blood cells that respond quickly to an infection.

White blood cell count
The number of white blood cells in a blood sample, determined through a laboratory blood test.

IMPORTANT SAFETY INFORMATION ABOUT ONIVYDE® (IRINOTECAN LIPOSOME INJECTION)

ONIVYDE can cause problems that can sometimes become serious or life threatening and can lead to death. Serious side effects may include fever and infection associated with a low white blood cell count (neutropenic fever, neutropenic sepsis); diarrhea, lung problems (interstitial lung disease, a group of diseases which cause inflammation of the lung tissues leading to scarring); and reactions during administration of ONIVYDE (including anaphylactic reactions). The most common side effects which were seen in people with pancreatic cancer treated with ONIVYDE include: diarrhea, feeling tired, vomiting, nausea, loss of appetite, inflammation in the mouth, fever, and dehydration. When taking ONIVYDE, you may also have abnormal blood test results. The most common blood cell count change seen in ONIVYDE-treated pancreatic cancer patients, is a reduction in the number of white blood cells, specifically lower lymphocytes and neutrophils (types of white blood cells), which are important for fighting infections.

Before you receive ONIVYDE, your healthcare provider will give you medications to decrease the potential for allergic reactions to infusion of ONIVYDE. You will also receive anti-nausea medicine to decrease nausea and vomiting, and, possibly, a medicine to decrease immediate diarrhea, called an anti-cholinergic.

What is ONIVYDE used for?

ONIVYDE is a prescription medicine used to treat pancreatic cancer, which has spread to other parts of the body. ONIVYDE can be used in patients who have already received gemcitabine treatment for their pancreatic cancer. ONIVYDE is given in combination with 2 other medicines, fluorouracil (also known as 5-FU) and leucovorin (which is often abbreviated as LV), and is not given alone.

When should ONIVYDE not be given?

You should not receive ONIVYDE if:

- you have had a **severe allergic reaction to ONIVYDE or irinotecan HCl**,
- your **white blood cell count is low** (neutrophil white blood cell count below the level of 1,500 cells/mm^3),
- you have **a fever and your neutrophil white blood cell count is low** (also called neutropenic fever), or
- you have a **problem in your bowel** that prevents food, fluids or gas from moving through your intestines.

Serious side effects may occur while taking ONIVYDE. Call or see your healthcare provider right away if you develop any of the following or if these get worse.

Serious side effects may include:

- **Infections (particularly if your white blood cells are low).** Symptoms of infection may include fever, chills, dizziness, or shortness of breath. Blood cell counts will be monitored periodically by your healthcare provider during treatment.
- **Diarrhea.** Symptoms of severe diarrhea may include persistent diarrhea; discolored stools (black, green or bloody); or symptoms of dehydration such as lightheadedness, dizziness, or faintness. Your healthcare provider may treat diarrhea with anti-diarrhea medicines (loperamide or atropine).
- **Lung problems (interstitial lung disease).** Symptoms of interstitial lung disease include new onset of cough or difficulty breathing and fever.
- **Allergic reaction (hypersensitivity).** Seek immediate medical attention for signs of severe reaction such as chest tightness; shortness of breath; wheezing; dizziness or faintness; or swelling of the face, eyelids, or lips when receiving or during the 24 hours after receiving ONIVYDE.

Please see accompanying full Prescribing Information, including Boxed Warnings for ONIVYDE®.

IMPORTANT SAFETY INFORMATION ABOUT ONIVYDE® (IRINOTECAN LIPOSOME INJECTION) (CONTINUED)

Getting medical treatment right away may keep these problems from becoming more serious.

Your healthcare provider will check you for these problems during treatment with ONIVYDE. Your healthcare provider may also need to delay or completely stop treatment with ONIVYDE, if you have severe side effects.

- The most frequent side effects resulting in **discontinuation** of ONIVYDE were diarrhea, vomiting, and infection caused by low white blood cells (neutropenic sepsis).
- The most frequent side effects requiring **dose reductions** of ONIVYDE were neutropenia, diarrhea, nausea, and low red blood cell count (anemia).
- The most frequent side effects requiring **dose interruptions or delays** of ONIVYDE were neutropenia, diarrhea, fatigue, vomiting, and low platelet counts called thrombocytopenia (platelets are important for clotting to stop bleeding).

Tell your healthcare provider about all the medicines you take, including:

- prescriptions
- over-the-counter medicines
- vitamins
- herbal supplements

Pregnancy and Nursing

If you are a female, tell your healthcare provider if you are pregnant or plan to become pregnant. ONIVYDE can harm your unborn baby. Females who are able to become pregnant should use an effective method of birth control during and for at least 1 month after the last dose of ONIVYDE. Talk to your healthcare provider about birth control methods that you can

Pregnancy and Nursing (continued)

use during this time. Tell your healthcare provider right away if you become pregnant during treatment with ONIVYDE. Before receiving ONIVYDE, tell your healthcare provider if you are breastfeeding or plan to breastfeed. It is not known if ONIVYDE passes into your breast milk. Do not breastfeed during treatment with ONIVYDE and for at least 1 month after the last dose of ONIVYDE.

If you are a man, you should not father a child during your treatment with ONIVYDE. ONIVYDE can harm the unborn baby of your partner. You should use an effective method of birth control during and for at least 4 months after the last dose of ONIVYDE.

These are not all the possible side effects of ONIVYDE.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. To learn more, talk to your healthcare provider. You can ask your doctor or pharmacist for information about ONIVYDE that is written for health professionals, and it can be found at ONIVYDE.com.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit fda.gov/medwatch or call 1-800-FDA-1088.

Please see accompanying full Prescribing Information, including Boxed Warnings for ONIVYDE®.

IPSEN
Innovation for patient care

August 2018 ONV-US-001402

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/mm^3 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).**

---------- 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/m^2 intravenous infusion over 90 minutes every two weeks. (2.2)
- Recommended starting dose of ONIVYDE in patients homozygous for UGT1A1*28 is 50 mg/m^2 every two weeks. (2.2)
- 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: 06/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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/mm^3 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 contra-indicated, 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/m^2 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/m^2 administered by intravenous infusion over 90 minutes. Increase the dose of ONIVYDE to 70 mg/m^2 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 [2ºC to 8ºC (36ºF to 46ºF)]. 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 to ONIVYDE or irinotecan HCl.

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/mm^3 or if neutropenic fever occurs. Resume ONIVYDE when the ANC is 1500/mm^3 or above. Reduce ONIVYDE dose for Grade 3-4 neutropenia or neutropenic fever following recovery in subsequent cycles *[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 HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction.

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/m^2 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 one month following the final 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/m^2 with leucovorin 400 mg/m^2 and fluorouracil 2400 mg/m^2 over 46 hours every 2 weeks (ONIVYDE/5-FU/LV; N=117), ONIVYDE 100 mg/m^2 every 3 weeks (N=147), or leucovorin 200 mg/m^2 and fluorouracil 2000 mg/m^2 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 ≥ 3 g/dL, and Karnofsky Performance Status (KPS) ≥ 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 (≥ 20%) of ONIVYDE were diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common, severe laboratory abnormalities (≥ 10% Grade 3 or 4) were lymphopenia and neutropenia. The most common serious adverse reactions (≥ 2%) of ONIVYDE were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

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 (≥5% difference for Grades 1-4 or ≥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 (≥5% Difference for Grades 1-4* or ≥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	38	17	15	10
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 (≥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.

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/m^2 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/m^2 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 final 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 one month after the final 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 final 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

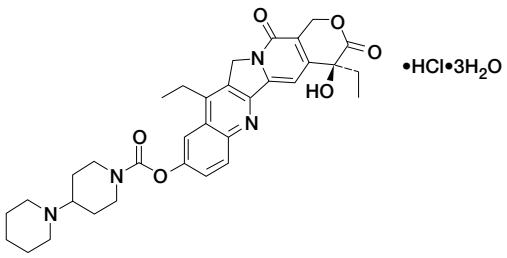
Of the 264 patients who received ONIVYDE as a single agent or in combination with 5-FU and leucovorin in Study 1, 49% were ≥ 65 years old and 13% were ≥ 75 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.

10 OVERDOSAGE

There are no treatment interventions known to be effective for management of overdosage 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-dioxo-1H-pyrano[3',4':6,7]-indolizino[1,2b]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/m^2 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/m^2 as a single agent or part of combination chemotherapy are presented in Table 4.

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

Dose (mg/m^2)	Total Irinotecan					Total SN-38		
	C_{max} [μg/mL] (n=25)	$AUC_{0-\infty}$ [h•μg/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)	$AUC_{0-\infty}$ [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
$AUC_{0-\infty}$: Area under the plasma concentration curve extrapolated to time infinity
$t_{½}$: Terminal elimination half-life
CL: Clearance
V_d: Volume of distribution

Over the dose range of 50 to 155 mg/m^2, 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/m^2) to 50% (300 mg/m^2).

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/m^2 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/m^2 [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/m^2) 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/m^2) 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/m^2 as an intravenous infusion over 90 minutes, followed by leucovorin 400 mg/m^2 intravenously over 30 minutes, followed by fluorouracil 2400 mg/m^2 intravenously over 46 hours, every 2 weeks. The ONIVYDE dose of 70 mg/m^2 is based on irinotecan 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 leucovorin 200 mg/m^2 intravenously over 30 minutes, followed by fluorouracil 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.

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% ≥ 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.

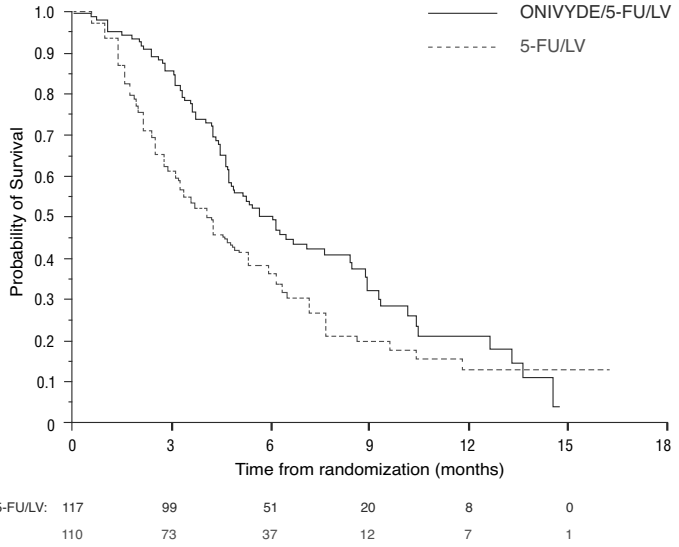
There was no improvement in overall survival for the ONIVYDE arm over the 5-FU/LV arm (hazard ratio=1.00, p-value=0.97 (two-sided log-rank test)).

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 2ºC to 8ºC (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 one month after the final 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 final 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 final dose *[see Use in Special Populations (8.2)]*.

Manufactured for:

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