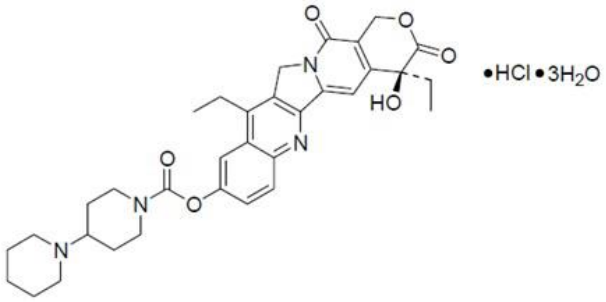
ONIVYDE pegylated liposomal (Irinotecan) 4.3 mg/ml concentrate for dispersion for infusion

1 DESCRIPTION

ONIVYDE pegylated liposomal is formulated with irinotecan hydrochloride trihydrate, a topoisomerase inhibitor, into a liposomal dispersion for intravenous use. The chemical name of irinotecan hydrochloride trihydrate is (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate, monohydrochloride, trihydrate. The empirical formula is $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$ and the molecular weight is 677.19 g/mole. The molecular structure is:



ONIVYDE pegylated liposomal 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.

2 DOSAGE FORM AND STRENGTHS

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

3 CLINICAL PHARMACOLOGY

3.1 Mechanism of Action

ONIVYDE pegylated liposomal is irinotecan (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.

3.2 Pharmacokinetics

The plasma pharmacokinetics of total irinotecan and total SN-38 were evaluated in patients with cancer who received ONIVYDE pegylated liposomal, 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 pegylated liposomal 70 mg/m^2 as a single agent or part of combination chemotherapy are presented in Table 1.

Table 1: 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}** [µg/mL] (n=25)	**$AUC_{0-\infty}$** [h.µg/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 extrapolated to time infinity
$t_{1/2}$: Terminal elimination half-life
CL: Clearance
V_d: Volume of distribution

Over the dose range of 50 to 155 mg/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 1.

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

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 pegylated liposomal 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.

3.3 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 pegylated liposomal 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 pegylated liposomal of 70 mg/m^2 [30 of 110 (27.3%)].

4 NONCLINICAL TOXICOLOGY

4.1 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 ONIVYDE pegylated liposomal. 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 pegylated liposomal 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 pegylated liposomal 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 pegylated liposomal).

5 CLINICAL STUDIES

The efficacy of ONIVYDE pegylated liposomal 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 pegylated liposomal plus fluorouracil/leucovorin (ONIVYDE pegylated liposomal/5-FU/LV), ONIVYDE pegylated liposomal, 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 pegylated liposomal/5-FU/LV received ONIVYDE pegylated liposomal 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 pegylated liposomal 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 pegylated liposomal as a single agent received ONIVYDE pegylated liposomal 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 pegylated liposomal at a reduced dose (50 mg/m^2 ONIVYDE pegylated liposomal, if given with 5-FU/LV or 70 mg/m^2 ONIVYDE pegylated liposomal as a single agent). When ONIVYDE pegylated liposomal was withheld or discontinued for adverse reactions, 5-FU was also withheld or discontinued. When the dose of ONIVYDE pegylated liposomal 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 pegylated liposomal versus 5-FU/LV and ONIVYDE pegylated liposomal/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 pegylated liposomal/5-FU/LV). The comparisons between the ONIVYDE pegylated liposomal/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 pegylated liposomal/5-FU/LV (N=117), ONIVYDE pegylated liposomal (N=151), or 5-FU/LV (N=149). Baseline demographics and tumor characteristics for the 236 patients randomized to ONIVYDE pegylated liposomal/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 pegylated liposomal/5-FU/LV arm over the 5-FU/LV arm as summarized in Table 2 and Figure 1.

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

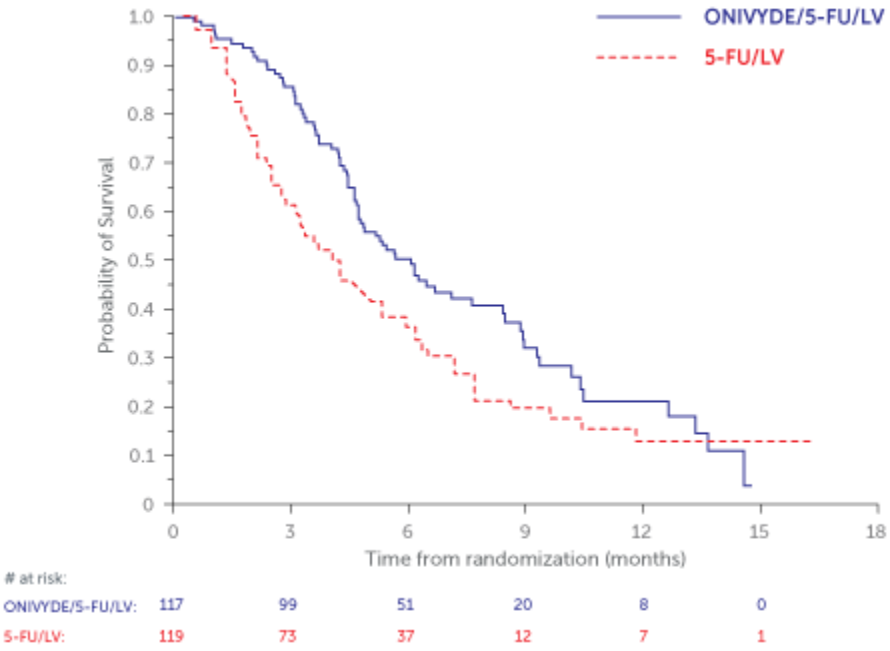
Table 2: Efficacy Results from Study 1[†]

	ONIVYDE pegylated liposomal/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% Confidence Interval)	(4.8, 8.5)	(3.3, 5.3)
Hazard Ration (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



6 INDICATION AND USAGE

ONIVYDE pegylated liposomal 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 pegylated liposomal is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas *[*see *Clinical Studies (5)]*.

7 CONTRAINDICATIONS

ONIVYDE pegylated liposomal is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE pegylated liposomal or irinotecan HCl.

8 WARNINGS AND PRECAUTIONS

WARNING: SEVERE NEUTROPENIA AND SEVERE DIARRHEA

Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE pegylated liposomal. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE pegylated liposomal in combination with fluorouracil and leucovorin. Withhold ONIVYDE pegylated liposomal for absolute neutrophil count below 1500/mm3 or neutropenic fever. Monitor blood cell counts periodically during treatment *[see Dosage and Administration (13.2) and Warnings and Precautions (8.1)]*.

**Severe diarrhea occurred in 13% of patients receiving ONIVYDE pegylated liposomal in combination with fluorouracil and leucovorin. Do not administer ONIVYDE pegylated liposomal to patients with bowel obstruction and chronic inflammatory bowel disease, until it is resolved. Withhold ONIVYDE pegylated liposomal for diarrhea of Grade 2 – 4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity *[see Dosage and Administration (13.2) and Warnings and Precautions*

General

ONIVYDE pegylated liposomal is liposomal formulation of irinotecan with different pharmacokinetics properties compared to non-liposomal irinotecan. The dose concentration and strength are different in comparison to non-liposomal irinotecans.

ONIVYDE pegylated liposomal is not equivalent to other non-liposomal irinotecan formulations and should not be interchanged.

In the limited number of patients with prior exposure to non-liposomal irinotecan, no benefit of ONIVYDE pegylated liposomal has been demonstrated.

8.1 Severe Neutropenia

ONIVYDE pegylated liposomal 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 pegylated liposomal, occurring in one of 117 patients in the ONIVYDE pegylated liposomal plus fluorouracil/leucovorin (ONIVYDE pegylated liposomal/5-FU/LV) arm and one of 147 patients receiving ONIVYDE pegylated liposomal as a single agent. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE pegylated liposomal/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 pegylated liposomal/5-FU/LV, and did not occur in patients receiving 5-FU/LV.

In patients receiving ONIVYDE pegylated liposomal/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 (3.3)]*.

Monitor complete blood cell counts on Days 1 and 8 of every cycle and more frequently if clinically indicated. Withhold ONIVYDE pegylated liposomal if the absolute neutrophil count (ANC) is below 1500/mm3 or if neutropenic fever occurs. Resume ONIVYDE pegylated liposomal when the ANC is 1500/mm3 or above. Sepsis with neutropenic fever and consequent septic shock with fatal outcome has been observed in patients with metastatic pancreatic adenocarcinoma treated with ONIVYDE pegylated liposomal. Reduce ONIVYDE pegylated liposomal dose for Grade 3-4 neutropenia or neutropenic fever following recovery in subsequent cycles *[see Dosage and Administration (13.2)]*.

Patients with severe bone marrow failure should not be treated with ONIVYDE pegylated liposomal.

History of prior abnormal radiation increases the risk of severe neutropenia and febrile neutropenia following ONIVYDE pegylated liposomal treatment. Close monitoring of blood counts is recommended, and the use of myeloid growth factors should be considered for patients with a history of abdominal radiation.

Caution should be exercised in patients receiving concurrent administration of ONIVYDE pegylated liposomal with irradiation.

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 pegylated liposomal.

Compared to Caucasian patients, Asian patients have an increased risk of severe and febrile neutropenia following treatment with ONIVYDE pegylated liposomal+5-FU/LV.

8.2 Immunosuppressive effects and vaccines

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic medicinal products including ONIVYDE pegylated liposomal 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.

8.3 Severe Diarrhea

ONIVYDE pegylated liposomal can cause severe and life-threatening diarrhea. Do not administer ONIVYDE pegylated liposomal to patients with bowel obstruction and chronic inflammatory bowel disease, until it is resolved.

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 Clinical Experience (9.1)]*. An individual patient may experience both early and late-onset diarrhea.

In Study 1, Grade 3 or 4 diarrhea occurred in 13% receiving ONIVYDE pegylated liposomal/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 pegylated liposomal/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 pegylated liposomal/5-FU/LV, compared to no Grade 3 or 4 early onset diarrhea in patients receiving 5-FU/LV. Of patients receiving ONIVYDE pegylated liposomal/5-FU/LV in Study 1, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea. Withhold ONIVYDE pegylated liposomal 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 pegylated liposomal at a reduced dose *[see Dosage and Administration (13.2)]*.

8.4 Cholinergic reactions

Early onset diarrhea may be accompanied by cholinergic symptoms such as rhinitis, increased salivation, flushing, diaphoresis, bradycardia, miosis and hyperperistalsis. In case of cholinergic symptoms atropine should be administered (unless clinically contraindicated).

8.5 Acute infusion and related infusions

Infusion reactions primarily consisting of rash, urticaria, periorbital edema or pruritus were reported in patients receiving ONIVYDE pegylated liposomal treatment. New events (all grade 1 or grade 2) occurred generally early during ONIVYDE pegylated liposomal treatment, with only 2 out of 10 patients noted with events after the fifth dose.

Hypersensitivity reactions, including acute infusion reaction, anaphylactic/anaphylactoid reaction and angioedema may occur. ONIVYDE pegylated liposomal should be discontinued in case of severe hypersensitivity reactions.

8.6 Prior Whipple Procedure

In the clinical study evaluating ONIVYDE pegylated liposomal+5-FU/LV, patients with a prior Whipple procedure has a higher of serious infections following treatment with ONIVYDE pegylated liposomal+5-FU/LV [9 of 29 (30%)] compared to 11 of 88 (12.5%) patients with no prior Whipple procedure. Patients should be monitored for signs of infections.

8.7 Vascular disorders

Onivyde pegylated liposomal 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.

8.8 Interstitial Lung Disease

Irinotecan HCl can cause severe and fatal interstitial lung disease (ILD). 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 pegylated liposomal therapy. A reticulo-nodular pattern on chest X-ray was observed in a small percentage of patients enrolled in a clinical study with irinotecan. Withhold ONIVYDE pegylated liposomal in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE pegylated liposomal in patients with a confirmed diagnosis of ILD.

8.9 Severe Hypersensitivity Reaction

Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE pegylated liposomal in patients who experience a severe hypersensitivity reaction.

8.10 Embryo-Fetal Toxicity

Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE pegylated liposomal, ONIVYDE pegylated liposomal 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 pegylated liposomal 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 pegylated liposomal and for seven months following the final dose *[see Use in Specific Populations (11.1, 11.3), Clinical Pharmacology (3.1)]*.

8.11 Patients with reduced UGT1A1 activity

Patients homozygous (UGT1A1*28/*28 or UGT1A1*6/*6) or heterozygous (UGT1A1*28/*6) in allele for UGT1A1*28 and/or UGT1A1*6 may be at increased risk for serious adverse reactions (especially neutropenia) caused by reduced glucurodination of SN-38. Added caution should be exercised when administering ONIVYDE pegylated liposomal in combination with 5-FU/LV in such patients. These patients should be monitored for hematologic toxicities.

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

In the clinical study evaluating ONIVYDE pegylated liposomal+5-FU/LV, 5 of 8 underweight patients experienced 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 pegylated liposomal in patients with body mass index <18.5 kg/m^2.

8.13 Excipients

This medicinal product contains 33.1 mg sodium per vial, equivalent to 1.65% of the WHO recommended maximum daily intake of 2g sodium for an adult.

9 ADVERSE REACTIONS

9.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of ONIVYDE pegylated liposomal 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 pegylated liposomal 70 mg/m^2 with leucovorin 400 mg/m^2 and fluorouracil 2400 mg/m^2 over 46 hours every 2 weeks (ONIVYDE pegylated liposomal/5-FU/LV; N=117), ONIVYDE pegylated liposomal 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 (5)]*. 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 pegylated liposomal/5-FU/LV arm, 9 weeks in the ONIVYDE pegylated liposomal monotherapy arm, and 6 weeks in the 5-FU/LV arm.

The most common adverse reactions (≥ 20%) of ONIVYDE pegylated liposomal 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 pegylated liposomal 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 pegylated liposomal in 11% of patients receiving ONIVYDE pegylated liposomal/5-FU/LV; the most frequent adverse reactions resulting in discontinuation of ONIVYDE pegylated liposomal were diarrhea, vomiting, and sepsis. Dose reductions of ONIVYDE pegylated liposomal for adverse reactions occurred in 33% of patients receiving ONIVYDE pegylated liposomal/5-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia. ONIVYDE pegylated liposomal was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE pegylated liposomal/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia.

Table 3 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 pegylated liposomal/5-FU/LV compared to patients who received 5-FU/LV.

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

Adverse Reaction	ONIVYDE pegylated liposomal/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
Vomitting	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 pegylated liposomal administration

‡ Late diarrhea: onset >1 day after ONIVYDE pegylated liposomal administration

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

♠ Includes febrile neutropenia

Cholinergic Reactions

ONIVYDE pegylated liposomal 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 pegylated liposomal-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 pegylated liposomal administration were reported in 3% of patients receiving ONIVYDE pegylated liposomal or ONIVYDE pegylated liposomal/5-FU/LV.

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

Table 4: Laboratory Abnormalities with Higher Incidence (≥5% Difference) in the ONIVYDE pegylated liposomal/5-FU/LV Arm*#

Laboratory abnormality	**ONIVYDE pegylated liposomal/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.

9.2 Post-Marketing Adverse Drug Reactions

The adverse reactions described in this section are derived from study data and post-marketing experience of Onivyde pegylated liposomal.

Immune system disorders: Anaphylactic/Anaphylactoid reaction, Angioedema

Skin and subcutaneous tissue disorders: Pruritus, Urticaria, Rash, Erythema

10 DRUG INTERACTIONS

10.1 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 pegylated liposomal therapy *[see Clinical Pharmacology (3.3)]*.

10.2 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 pegylated liposomal with other inhibitors of CYP3A4 (e.g., clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 (e.g., atazanavir, gemfibrozil, indinavir, regorafenib) 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 pegylated liposomal therapy *[see Clinical Pharmacology (3.3)]*.

10.3 Antineoplastic agents (including flucytosine as a prodrug for 5-fluorouracil)

Adverse effects of irinotecan, such as myelosuppression, may be exacerbated by other antineoplastic agents having a similar adverse-effect profile.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE pegylated liposomal, ONIVYDE pegylated liposomal can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (3.1)]*. 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 pegylated liposomal 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 pegylated liposomal 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 pegylated liposomal 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.

11.2 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 pegylated liposomal, advise a nursing woman not to breastfeed during treatment with ONIVYDE pegylated liposomal 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.

11.3 Females and Males of Reproductive Potential

Fertility

There are no data on the impact of ONIVYDE pegylated liposomal on human fertility. Non liposomal irinotecan was shown to cause atrophy of male and female reproductive organs after multiple daily irinotecan doses in animals (see section 4.1). Prior to starting the administration of ONIVYDE pegylated liposomal consider advising patients on the preservation of gametes.

Contraception

Females
ONIVYDE pegylated liposomal can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (11.1)]*. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE pegylated liposomal and for seven months 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 pegylated liposomal and for four months after the final dose *[see Nonclinical Toxicology (4.1)]*.

11.4 Pediatric Use

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

11.5 Geriatric Use

Of the 264 patients who received ONIVYDE pegylated liposomal 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.

11.6 Patients with reduced UGT1A1 Activity

For more information, see Warnings and Precautions (8.10)

12 OVERDOSAGE

There are no treatment interventions known to be effective for management of overdosage of ONIVYDE pegylated liposomal.

13 DOSAGE AND ADMINISTRATION

13.1 Important Use Information

DO NOT SUBSTITUTE ONIVYDE pegylated liposomal for other drugs containing irinotecan HCl.

13.2 Recommended Use

Administer ONIVYDE pegylated liposomal prior to leucovorin and fluorouracil *[see Clinical Studies (5)]*.

• The recommended dose of ONIVYDE pegylated liposomal is 70 mg/m^2 administered by intravenous infusion over 90 minutes every 2 weeks.

• A reduced starting dose of ONIVYDE pegylated liposomal of 50 mg/m^2 should be considered in patients known to be homozygous for the UGT1A1*28 allele. A dose increase of ONIVYDE pegylated liposomal to 70 mg/m^2 should be considered if tolerated in subsequent cycles.

• There is no recommended dose of ONIVYDE pegylated liposomal for patients with serum bilirubin above the upper limit of normal *[see Adverse Reactions (9.1) and Clinical Studies (5)]*.

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

13.3 Dose Modifications for Adverse Reactions

All dose modifications should be based on the worst preceding toxicity. LV dose does not require adjustment. For Grade 1 and 2 toxicities, there are no dose modifications recommended. Dose adjustments, as summarized in Table 5 and Table 6, are recommended to manage Grade 3 or 4 toxicities related to ONIVYDE pegylated liposomal.

For patients who start treatment with 50 mg/m^2 ONIVYDE pegylated liposomal 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.

Patients who are known to be homozygous for UGT1A1*28 and without drug related toxicities during the first cycle of therapy (reduced dose of 50 mg/m^2) may have the dose of ONIVYDE pegylated liposomal increased to a total dose of 70 mg/m^2 in subsequent cycles based on individual patient tolerance.

Table 5: Recommended dose modifications for ONIVYDE pegylated liposomal+5-FU/LV for Grade 3-4 toxicities for patients not homozygous for UGT1A1*28

Toxicity grade (value) by NCI CTCAE v4.0[1]	**ONIVYDE pegylated liposomal/5-FU adjustment (for patients not homozygous for UGT1A1*28**	
Hematological toxicities		
Neutropenia	A new cycle of therapy should not begin until the absolute neutrophil count is ≥ 1500/mm^3	
***Grade 3 or Grade 4 (<1000/mm^3) or* Neutropenic fever**	***First occurrence***	Reduce ONIVYDE pegylated liposomal dose to 50mg/m^2 Reduce 5-FU dose by 25% (1800 mg/m^2).
	Second occurrence	Reduce ONIVYDE pegylated liposomal dose to 43 mg/m^2 Reduce 5-FU dose by an additional 25% (1350mg/m^2)
	Third occurrence	Discontinue treatment
Thrombocytopenia **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 CTCAE toxicity grading and are the same as recommended for neutropenia above.	
Non-hematological toxicities[2]		

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 2	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	***First occurrence***	Reduce ONIVYDE pegylated liposomal dose to 50 mg/m^2 Reduce 5-FU dose by 25% (1800 mg/m^2)
	Second occurrence	Reduce ONIVYDE pegylated liposomal dose to 43 mg/m^2 Reduce 5-FU dose by an additional 25% (1350 mg/m^2)
	Third occurrence	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 occurrence***	Optimize antiemetic therapy Reduce ONIVYDE pegylated liposomal dose to 50 mg/m^2
	Second occurrence	Optimize antiemetic therapy Reduce ONIVYDE pegylated liposomal dose to 43 mg/m^2
	Third occurrence	Discontinue treatment
Hepatic, renal, respiratory or other[2] toxicities ***Grade 3 or 4***	A new cycle of therapy should not begin until the adverse reaction resolves to ≤ Grade 1	
	First occurrence	Reduce ONIVYDE pegylated liposomal dose to 50 mg/m^2 Reduce 5-FU dose by 25% (1800 mg/m^2)
	Second occurrence	Reduce ONIVYDE pegylated liposomal dose to 43 mg/m^2 Reduce 5-FU dose by an additional 25% (1350 mg/m^2)
	Third occurrence	Discontinue treatment
Anaphylactic reaction	***First occurrence***	Discontinue treatment

1 NCI CTCAE v 4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0
2 Excludes asthenia and anorexia; Asthenia and Grade 3 anorexia do not require dose adjustment.

Table 6: Recommended dose modifications for ONIVYDE pegylated liposomal+5-FU/LV for Grade 3-4 toxicities for patients homozygous for UGT1A1*28

Toxicity grade (value) by NCI CTCAE v4.0[1]	**ONIVYDE pegylated liposomal/5-FU adjustment (for patients homozygous for UGT1A1*28 without previous increase to 70 mg/m^2)**	
Adverse reactions[2] ***Grade 3 or Grade 4***	A new cycle of therapy should not begin until adverse event resolves to ≤ Grade 1	
	First occurrence	Reduce ONIVYDE pegylated liposomal dose to 43 mg/m^2 5-FU dose modification as in Table 5
	Second occurrence	Reduce ONIVYDE pegylated liposomal dose to 35 mg/m^2

		5-FU dose modification as in Table 5
	Third occurrence	Discontinue treatment

1 NCI CTCAE v 4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0
2 Excludes asthenia and anorexia; Asthenia and Grade 3 anorexia do not require dose adjustment.

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

13.4 Preparation and Administration

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

Preparation

• Withdraw the calculated volume of ONIVYDE pegylated liposomal from the vial using a needle not larger than 21 gauge. Dilute ONIVYDE pegylated liposomal in 500 mL 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP and mix diluted dispersion by gentle inversion.

• Protect diluted dispersion from light.

• Chemical and physical stability for the diluted dispersion for infusion has been demonstrated at 15°C to 25°C for up to 4 hours or in the refrigerator (2°C to 8°C) for not more than 24 hours. Allow diluted dispersion to come to room temperature prior to administration. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

• Do NOT freeze.

Administration

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

14 HOW SUPPLIED/STORAGE AND HANDLING

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

NDC: 69171-398-01

Storage and Handling
Store ONIVYDE pegylated liposomal at 2ºC to 8ºC (36°F to 46°F). Do NOT freeze. Protect from light.

ONIVYDE pegylated liposomal is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

15 PATIENT COUNSELLING 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 (8.1)]*.

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 (8.3)]*.

Vascular Disorders
Inform patients of the risk of thromboembolism. Advise patients to contact their healthcare provider if they experience signs or symptoms of a blood clot, like sudden pain and swelling in a leg or an arm, sudden onset of coughing, chest pain or difficulty breathing.

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 (8.8)]*.

Hypersensitivity to irinotecan HCl or ONIVYDE pegylated liposomal
Advise patients of the potential risk of severe hypersensitivity and that ONIVYDE pegylated liposomal is contraindicated in patients with a history of severe allergic reactions with irinotecan HCl or ONIVYDE pegylated liposomal. 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 (7) and Warnings and Precautions (8.9)]*.

Females and males of reproductive potential

Embryo-fetal toxicity

Inform females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment and for seven months after the final dose, and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (8.10), Use in Specific Populations (11.1, 11.3)]*.

Contraception
Advise male patients with female partners of reproductive potential to use condoms during treatment with ONIVYDE pegylated liposomal and for four months after the final dose *[see Females and Males of Reproductive Potential 11.3)]*.

Lactation
Advise women not to breastfeed during treatment with ONIVYDE pegylated liposomal and for one month after the final dose *[see Use in Special Populations (11.2)]*.

16 REFERENCES

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

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