Do not substitute ONIVYDE for or with other medicine products containing irinotecan. ONIVYDE is not equivalent to non-liposomal irinotecan formulations and should not be interchanged

1 ONIVYDE 4.3 mg/mL concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Irinotecan-anhydrous free base (nanoliposomal) 4.3 mg/mL.

One 10 mL vial of concentrate contains 43 mg irinotecan anhydrous free base at a concentration of 4.3 mg/mL, which is equivalent to 50 mg irinotecan hydrochloride trihydrate at a concentration of 5 mg/mL.

One mL of concentrate contains 4.3 mg irinotecan anhydrous free base at a concentration of 4.3 mg/mL, which is equivalent to 5 mg irinotecan hydrochloride trihydrate at a concentration of 5 mg/mL.

Excipient with known effect
Each mL of ONIVYDE contains 0.144 mmol sodium, which is 3.31 mg sodium. This fact should be taken into consideration by patients on a controlled sodium diet (See section 4.4).

For the full list of excipients (see section 6.1).

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

ONIVYDE is supplied as a sterile, white to slightly yellow opaque isotonic liposomal dispersion for intravenous use.

The solution is buffered at pH 7.25. The osmolality of the formulation is 280-310 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and folinic acid (leucovorin) in adult patients who have been previously treated with a gemcitabine based therapy.

4.2 Dose and method of administration

ONIVYDE must only be prescribed and administered to patients by healthcare professionals experienced in the use of anti-cancer therapies.

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

DO NOT SUBSTITUTE ONIVYDE for or with other drug products containing irinotecan.

DILUTE ONIVYDE prior to administration.

FOR INTRAVENOUS USE ONLY.ONIVYDE treatment should continue until the development of disease progression or unacceptable toxicity.

Preparation of the solution and administration

ONIVYDE is supplied as a sterile liposomal dispersion at a concentration of 4.3 mg/mL and must be diluted prior to administration using a needle not larger than 21 gauge. Dilute with 5 % w/v glucose solution for injection or 0.9 % sodium chloride solution for injection to prepare a solution of the appropriate dose of ONIVYDE diluted to a final volume of 500 mL. Mix diluted solution by gentle inversion.

Do not use any in-line filters.

ONIVYDE should be administered before LV followed by 5-FU. ONIVYDE must not be administered as a bolus injection or an undiluted solution.

Aseptic techniques must be followed during the preparation of the infusion. ONIVYDE is for single use only.

From a microbiological point of view, the product should be used as soon as possible after dilution, but may be stored at ambient temperature for up to 6 hours. The diluted solution for infusion can be stored in the refrigerator (2 °C to 8 °C) for no more than 24 hours prior to use. Protect diluted solution from light. Do not freeze diluted solution.

Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with normal saline and/or sterile water and applications of ice are recommended.

Dosage

ONIVYDE, leucovorin (LV) and 5-fluorouracil (5-FU) should be administered sequentially. The recommended dose and regimen of ONIVYDE is 70mg/m^2 intravenously over 90 minutes, followed by leucovorin (LV) 400mg/m^2 intravenously over 30 minutes, followed by 5-FU 2400mg/m^2 intravenously over 46 hours, administered every 2 weeks.

A reduced starting dose should be considered of ONIVYDE 50mg/m^2 for patients known to be homozygous for the UGT1A1*28 allele as they may have an increased risk for developing neutropenia based on experience with non-liposomal irinotecan therapy. In the clinical study evaluating ONIVYDE in combination with 5-FU and leucovorin, patients homozygous for the UGT1A1*28 allele received a starting dose of 50 mg/m^2 and did not experience a greater incidence of Grade 3 or 4 neutropenia than those not homozygous.

Dosage adjustments
Subsequent doses of ONIVYDE and 5-FU should be adjusted as suggested in Table 1. All dose modifications should be based on the worst preceding toxicity. Leucovorin dose does not require adjustment. For Grade 1 and 2 toxicities there are no dose modifications recommended. Dose adjustments, as summarised in Table 1, are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia, or other Grade 3 or 4 toxicities judged to be related to ONIVYDE.

For patients who start treatment with 50mg/m^2 ONIVYDE and do not dose escalate to 70mg/m^2, the recommended first dose reduction is to 43mg/m^2 and the second dose reduction is to 35mg/m^2. Patients who require further dose reduction should discontinue treatment.

Patients who are known to be homozygous for UGT1A1*28 and without medicine- related toxicities during the first cycle of therapy (if initiated at a reduced dose of 50mg/m^2) may have the dose of ONIVYDE increased to a total dose of 70mg/m^2 in subsequent cycles based on individual patient tolerance (See section 4.8 and 5.1).

Table 1: Recommended Dose Modifications for ONIVYDE + 5-FU/LV for Grade 3 - 4 toxicities		
Toxicity ***NCI CTC Grade[1] (Value)***	**ONIVYDE/5-FU adjustment**	
Haematological 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 dose to 50mg/m^2 Reduce 5-FU dose by 25% (1800mg/m^2).
	Second Occurrence	Reduce ONIVYDE dose to 43mg/m^2 Reduce 5-FU dose by an additional 25% (1350mg/m^2).
	Third occurrence	Discontinue treatment
Thrombocytopenia	A new cycle of therapy should not begin until the platelet count is ≥ 100,000/mm^3	
Leukopenia	Dose modifications for leukopenia and thrombo-cytopenia are based on NCI toxicity grading and are the same as recommended for neutropenia above.	
Nonhaematological toxicities[2]:		
Diarrhoea	A new cycle of therapy should not begin until diarrhoea resolves to ≤ Grade 1 (2 - 3 stools/day more than pre-treatment frequency).	
Grade 3 or 4 *(7 - 9 stools/day >pretreatment or > 10 stools/day > pretreatment)*	**First occurrence**	Reduce ONIVYDE dose to 50mg/m^2 Reduce 5-FU dose by 25% (1800mg/m^2)
	Second occurrence	Reduce ONIVYDE dose to 43mg/m^2 Reduce 5-FU dose by an additional 25%(1350mg/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 dose to 50mg/m^2
	Second occurrence	Optimize antiemetic therapy Reduce ONIVYDE dose to 43mg/m^2
	Third occurrence	Discontinue treatment
Hepatic, renal, respiratory or other[2] toxicities *Grade 3 or 4*	**First occurrence**	Reduce ONIVYDE dose to 50g/m^2 Reduce 5-FU dose by 25% (1800mg/m^2)
	Second occurrence	Reduce ONIVYDE dose to 43mg/m^2 Reduce 5-FU dose by an additional 25% (1350mg/m^2)
	Third occurrence	Discontinue treatment

[1] NCI CTC version 4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0

[2] Excludes asthenia and anorexia. Asthenia and Grade 3 anorexia does not require dose adjustment.

Premedication
It is recommended that patients receive premedication for nausea and vomiting prior to ONIVYDE infusion with standard doses of dexamethasone (or an equivalent corticosteroid) together with a 5-HT3 antagonist (or other anti-emetic), unless contraindicated for the individual patient. Premedication should be given on the day of treatment, starting at least 30 minutes before administration of ONIVYDE. Atropine may be prescribed prophylactically for patients who experienced acute cholinergic symptoms in previous cycles. Physicians should also consider providing patients with an antiemetic regimen for subsequent use, as well as loperamide (or equivalent) for treatment of late diarrhoea, if necessary.

Special populations

Patients with hepatic impairment
There is no experience of ONIVYDE in patients with bilirubin levels > 2mg/dL. Dosing for patients with bilirubin level > 2mg/dL is not recommended due to insufficient clinical information in these patients (See section 4.4).

Patients with renal impairment
No dose adjustment is recommended in patients with mild to moderate renal impairment (see sections 4.4 and 5.2). ONIVYDE is not recommended for use in patients with severe renal impairment (CLcr < 30 mL/min).

Elderly
Forty-one percent (41%) of patients treated with ONIVYDE across the clinical program were ≥ 65 years. No dose adjustment is recommended.

Paediatric use
There is no relevant use of ONIVYDE in the paediatric population in the treatment of pancreatic cancer. The safety and efficacy of ONIVYDE in patients under the age of 18 years has not been established.

Method of Administration
ONIVYDE is for intravenous use only. The concentrate must be diluted prior to administration and given as single intravenous infusion over 90 minutes. For more details see section 6.6.

Precautions to be taken before handling or administering the medicinal product
ONIVYDE is a cytotoxic medicinal product. The use of gloves, goggles and protective clothing when handling or administering ONIVYDE is recommended. Pregnant staff should not handle ONIVYDE.

4.3 Contraindications

ONIVYDE is contraindicated in patients with hypersensitivity to irinotecan or to any of the excipients (see section 6.1.).

4.4 Special warnings and precautions for use

General
ONIVYDE is a nanoliposomal formulation of irinotecan with altered pharmacokinetic properties compared to non-liposomal irinotecan. The dose concentration and strength is different to non-liposomal irinotecans. Do not substitute for or with other irinotecan formulations.

Myelosuppression/Neutropenia
Death due to sepsis following neutropenia has been reported in patients treated with ONIVYDE. In NAPOLI-1 study, neutropenic fever/sepsis (defined as febrile neutropenia or neutropenic sepsis) occurred in 4 out of 117 patients (3.4%) receiving ONIVYDE plus fluorouracil/leucovorin. Withhold treatment if neutropenic fever occurs or the absolute neutrophil count drops below 1500/mm^3. Manage neutropenic fever promptly with antibiotic support. Resume treatment after recovery to an absolute neutrophil count $\geqslant$ 1500/mm^3 at reduced doses (see section 4.2.).

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

Patients with baseline serum total bilirubin levels of greater than 2mg/dL were excluded from ONIVYDE clinical trials. Patients with deficient glucuronidation of bilirubin, such as those with Gilbert's syndrome, may be at greater risk of myelosuppression when receiving therapy with ONIVYDE.

Diarrhoea and cholinergic reactions
Diarrhoea can occur. Late onset diarrhoea, typically appearing more than 24 hours after treatment, can be debilitating and, on rare occasions, life threatening since persistent loose or watery stools can result in dehydration, electrolyte imbalance or sepsis. Diarrhoea may be complicated by colitis, ulceration, bleeding ileus, colon obstruction, and infection.

In NAPOLI-1 study, Grade 3 or 4 diarrhoea occurred in 15 out of 117 patients (12.8%) receiving ONIVYDE plus fluorouracil/leucovorin. For patients experiencing late diarrhoea, the median time to late diarrhoea onset was 8 days from the previous dose of ONIVYDE.

Initiate loperamide at first occurrence of poorly formed or loose stools or at the earliest onset of bowel movements more frequent than normal and give until patient is without diarrhoea for at least 12 hours. If diarrhoea persists while patient is on loperamide for more than 24 hours, consider adding oral antibiotic support (fluoroquinolone for 7 days). Loperamide should not be used for more than 48 consecutive hours due to risk of paralytic ileus. If diarrhoea persists more than 48 hours, stop loperamide, monitor and replace fluid electrolytes and continue antibiotic support until resolution for accompanying symptoms. Delay ONIVYDE treatment until diarrhoea resolves to $\leq$ Grade 1 (2 - 3 stools/day more than pre-treatment frequency). Do not administer ONIVYDE to patients with bowel obstruction, until it is resolved. Following Grade 3 or 4 diarrhoea, the subsequent dose of ONIVYDE and fluorouracil should be reduced (see section 4.2.).

Early onset diarrhoea, typically appearing during or shortly after treatment, can occur but is infrequent and usually transient. Early onset diarrhoea may also be accompanied by cholinergic symptoms that can include rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis and intestinal hyperperistalsis that can induce abdominal cramping. In NAPOLI-1 study, early onset diarrhoea (diarrhoea onset within 1 day of ONIVYDE administration) occurred in 35 patients (30%) and cholinergic events occurred in 4 patients (3.4%) receiving ONIVYDE plus fluorouracil/leucovorin. Consider prophylactic or therapeutic treatment with atropine in patients experiencing cholinergic symptoms (0.25mg to 1mg, administered intravenously or subcutaneously), unless contraindicated.

The frequency of diarrhoea was higher and more severe in Caucasian patients than in Asian patients (Grade 3 or higher diarrhoea 19% vs 3%, respectively) when treated with ONIVYDE plus 5-fluorouracil/leucovorin.

Acute infusion and related reactions
Infusion reactions primarily consisting of rash, urticaria, periorbital oedema or pruritus were reported in patients receiving ONIVYDE treatment. New events (all grade 1 or grade 2) occurred generally early during ONIVYDE treatment, with only 2 out of 10 patients noted with events after the fifth dose. Hypersensitivity reactions, including acute infusion reaction, anaphylactic reaction, anaphylactoid reaction and angioedema may occur. ONIVYDE should be discontinued in case of severe hypersensitivity reactions.

Prior Whipple procedure
Patients with a history of a Whipple procedure have a higher risk of serious infections following ONIVYDE treatment in combination with 5-FU and leucovorin (see section 4.8 - *Adverse effects (Undesirable effects)*). Patients should be monitored for signs of infections.
Risk of neutropenia in patients with homozygous UGT1A1 Activity
Individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7 / 7 genotype) have an increased risk for developing neutropenia following non-liposomal irinotecan therapy. Consider a reduced starting dose of ONIVYDE of 50 mg/m^2 for patients known to be homozygous for the UGT1A1*28 allele. Patients without medicine related toxicities during the first 2 weeks of therapy may have their dose of ONIVYDE increased to 70 mg/m^2 based on individual patient tolerance (see sections 4.2. and 5.2).

In NAPOLI-1 study, patients homozygous for the UGT1A1*28 allele did not experience a greater incidence of Grade 3 or 4 neutropenia than those not homozygous (2 out of 7 patients [28.6%] vs 30 of 110 patients [27.3%], respectively).

Performance status
Clinical trials with ONIVYDE were conducted in patients with a performance status of KPS ≥70 (see section 5.1).

Hepatic impairment
No hepatic impairment study has been conducted with ONIVYDE. In clinical studies of non-liposomal irinotecan administered on a weekly dosage schedule, patients with modestly elevated baseline serum total bilirubin levels (1.0 to 2.0mg/dL) had a significantly greater likelihood of experiencing first cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0mg/dL. Use caution in patients with hepatic impairment, particularly in those with bilirubin > 1mg/dL (see section 5.2).

Impaired renal function
No dedicated pharmacokinetic study has been conducted in patients with renal impairment. 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), 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.

Irradiation therapy
History of prior abdominal radiation increases the risk of severe neutropenia and febrile neutropenia following ONIVYDE 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 with irradiation.

Immunosuppressant effects and vaccines
Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents, including ONIVYDE, may result in serious or fatal infections.

Vaccination with a live vaccine should be avoided in patients receiving irinotecan. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Vascular disorders

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

Interstitial Lung Disease
Interstitial Pulmonary Disease (IPD)-like events, including fatalities, have occurred in patients receiving irinotecan HCl. New or progressive dyspnoea, cough, and fever should prompt interruption of chemotherapy, pending diagnostic evaluation.

While IPD-like events have not been observed with ONIVYDE to date, if IPD is diagnosed, ONIVYDE and other chemotherapy should be discontinued and appropriate treatment instituted as needed.

Patients on controlled sodium diet
Each mL of ONIVYDE contains 0.144 mmol sodium, which is 3.31 mg sodium. This fact should be taken into consideration by patients on a controlled sodium diet.

Use in the elderly
Forty one percent (41%) of patients treated with ONIVYDE in clinical studies were 65 years and older. Overall, no differences in safety or efficacy were reported between patients 65 years and older and patients less than 65 years.

4.5 Interaction with other medicines and other forms of interaction

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

Fluorouracil (5-FU) and leucovorin (LV)
Based on the population PK analysis, the pharmacokinetics of ONIVYDE are not altered by the co-administration of fluorouracil/leucovorin.

Strong CYP3A4 inducers
Exposure to irinotecan and its active metabolite SN-38 is substantially reduced in patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin, phenobarbital or carbamazepine. The appropriate starting dose for patients taking these anticonvulsants or other strong inducers such as rifampicin and rifabutin and St. John´s wort has not been defined. Consideration should be given to substituting non-enzyme inducing therapies at least 2 weeks prior to initiation of ONIVYDE therapy. Strong CYP3A4 inducers should not be administered with ONIVYDE unless there are no therapeutic alternatives.

Strong CYP3A4 or UGT1A1 inhibitors
Patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan and its active metabolite SN-38. Coadministration of ONIVYDE with other inhibitors of CYP3A4 (e.g. grapefruit juice, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprvir, voriconazole) or UGT1A1 (e.g. atazanavir,

gemfibrozil, indinavir may increase systemic exposure to irinotecan or SN-38). Strong CYP3A4 inhibitors should be discontinued at least 1 week prior to starting ONIVYDE therapy. Strong CYP3A4 or UGT1A1 inhibitors should not be administered with ONIVYDE unless there are no therapeutic alternatives.

Other interactions

Neuromuscular blocking agents
Interaction between ONIVYDE and neuromuscular blocking agents was not studied. Since irinotecan has anticholinesterase activity, the neuromuscular blocking effects of suxamethonium may be prolonged and the neuromuscular blockade of non-depolarising medicines may be antagonised

Prochlorperazine
Prochlorperazine is a CYP3A4 inhibitor that is used as an antiemetic, particularly for nausea and vomiting caused by chemotherapy. Therefore, co-administration of ONIVYDE with other inhibitors of CYP3A4 may increase systemic exposure of irinotecan and SN-38.

Laxatives
Interaction between ONIVYDE and laxatives was not studied; however, it would be expected that the incidence and/or severity of diarrhoea would be worsened by laxative use during therapy with ONIVYDE.

Diuretics
In view of the potential risk of dehydration secondary to vomiting and/or diarrhoea induced by ONIVYDE, consideration should be given to withholding diuretics during dosing with ONIVYDE, particularly during periods of active vomiting or diarrhoea.

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

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

4.6 Fertility, pregnancy and lactation

Effects on fertility
Dedicated fertility studies have not been performed with ONIVYDE. For irinotecan, in animals, adverse effects on the fertility of offspring have been documented. Prior to starting the administration of ONIVYDE pegylated liposomal consider advising patients on the preservation of gametes. Irinotecan is known to cause atrophy of male reproductive organs after multiple daily irinotecan doses in animals.

Atrophy of male and female reproductive organs was observed in rats and/or dogs receiving irinotecan liposome injection every 3 weeks at doses equal to or greater than 75 and 21 mg/kg, respectively (approximately 52 and 6 times the clinical exposure to irinotecan and 195 and 0.3 times to the active metabolite SN-38, at the clinical ONIVYDE dose of 70 mg/m^2, based on AUC).

No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of un-encapsulated irinotecan hydrochloride in doses of up to 6 mg/kg/day to rats. Atrophy of male reproductive organs was observed after multiple daily irinotecan hydrochloride doses both in rodents at 20 mg/kg and dogs at 0.4 mg/kg.

Use in pregnancy
Category D
There are no adequate data on the use of ONIVYDE in pregnant women. ONIVYDE can cause harm to the foetus when administered to the pregnant woman as the main ingredient irinotecan has been shown to be embryotoxic and teratogenic in animals (see section 5.3). Therefore, based on results from animal studies and the mechanism of action of irinotecan, ONIVYDE should not be used during pregnancy unless clearly necessary. If ONIVYDE is used during pregnancy or if the patient becomes pregnant while receiving therapy, the patient should be informed about the potential hazard to the foetus.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving ONIVYDE therapy. Women should use effective contraception during ONIVYDE treatment and 7 months thereafter. Males should be advised not to father children while receiving ONIVYDE. Males should use condoms during ONIVYDE treatment and 4 months thereafter.

Intravenous administration of 6 mg/kg/day irinotecan hydrochloride to rats and rabbits during the period of organogenesis, is embryotoxic as characterised by increased post-implantation loss and decreased numbers of live foetuses. Irinotecan hydrochloride was teratogenic in rats at doses greater than 1.2 mg/kg/day and in rabbits at 6.0 mg/kg/day. Teratogenic effects included a variety of external, visceral, and skeletal abnormalities.

Use in lactation
It is unknown whether ONIVYDE/or its metabolites are excreted into human milk. Because of the potential for serious adverse reactions in nursing infants from ONIVYDE, breast-feeding should be discontinued when receiving therapy with ONIVYDE.

In lactating rats, radioactivity appeared in milk within 5 minutes of intravenous administration of radiolabelled irinotecan hydrochloride and was concentrated up to 65-fold at 4 hours relative to plasma concentrations. Irinotecan hydrochloride administered to rat dams for the period following organogenesis through weaning at doses of 6.0 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

In a clinical trial, 147 patients with metastatic adenocarcinoma of the pancreas received ONIVYDE ($100mg/m^2$) as monotherapy and 117 received ONIVYDE ($70mg/m^2$) in combination with 5-FU/LV.

The most common adverse reactions (incidence ≥ 20%) seen with ONIVYDE in combination with 5-fluorouracil and leucovorin were: diarrhoea, nausea, vomiting, decreased appetite, neutropenia, fatigue, anaemia, stomatitis and pyrexia.

The most common serious adverse reactions (≥ 2%) of ONIVYDE therapy were diarrhoea, vomiting, febrile neutropenia, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

Rates of adverse events leading to permanent discontinuation of all study therapy were 11% for the ONIVYDE + 5-FU/LV arm and 12% for the monotherapy arm. The most frequently reported adverse reactions leading to discontinuation were infection and diarrhoea for ONIVYDE+5 FU/LV arm and vomiting and diarrhoea for the monotherapy arm. Table 2 reports adverse events reported in the clinical trial at a frequency of 10% or more.

Table 2: Adverse Events Reported in the NAPOLI-1 Study at a Frequency of ≥ 10%

MedDRA Standard System Organ Class	**ONIVYDE (N=147) n (%)**	**ONIVYDE+5-FU/LV (N=117) n (%)**	**5-FU/LV (N=134) n (%)**
Number of subjects with any TEAE(s)	145 (98.6)	116 (99.1)	132 (98.5)
Gastrointestinal disorders			
Diarrhoea	103 (70.1)	69 (59.0)	35 (26.1)
Nausea	89 (60.5)	60 (51.3)	46 (34.3)
Vomiting	80 (54.4)	61 (52.1)	35 (26.1)
Abdominal pain	50 (34.0)	27 (23.1)	42 (31.3)
Constipation	26 (17.7)	26 (22.2)	32 (23.9)
Abdominal pain upper	17 (11.6)	11 (9.4)	10 (7.5)
Stomatitis	5 (3.4)	16 (13.7)	8 (6.0)
General disorders and administration site conditions			
Fatigue	54 (36.7)	47 (40.2)	37 (27.6)
Asthenia	35 (23.8)	24 (20.5)	22 (16.4)
Pyrexia	29 (19.7)	27 (23.1)	15 (11.2)
Oedema peripheral	28 (19.0)	13 (11.1)	20 (14.9)
Mucosal inflammation	8 (5.4)	12 (10.3)	5 (3.7)
Metabolism and nutrition disorders			
Decreased appetite	72 (49.0)	52 (44.4)	43 (32.1)
Hypokalaemia	32 (21.8)	14 (12.0)	12 (9.0)
Hypomagnesaemia	20 (13.6)	7 (6.0)	5 (3.7)
Hypoalbuminaemia	19 (12.9)	7 (6.0)	8 (6.0)
Dehydration	15 (10.2)	9 (7.7)	9 (6.7)
Investigations			
Weight decreased	29 (19.7)	20 (17.1)	9 (6.7)
Neutrophil count decreased	15 (10.2)	17 (14.5)	2 (1.5)
White blood cell count decreased	10 (6.8)	17 (14.5)	2 (1.5)
Platelet count decreased	3 (2.0)	12 (10.3)	3 (2.2)
Blood and lymphatic system disorders			
Anaemia	48 (32.7)	44 (37.6)	31 (23.1)
Neutropenia	22 (15.0)	27 (23.1)	4 (3.0)
Leukopenia	6 (4.1)	12 (10.3)	1 (0.7)
Skin and subcutaneous tissue disorders			
Alopecia	32 (21.8)	16 (13.7)	6 (4.5)
Nervous system disorders			
Dizziness	17 (11.6)	15 (12.8)	13 (9.7)
Musculoskeletal and connective tissue disorders			
Back pain	12 (8.2)	15 (12.8)	16 (11.9)

The adverse reactions described in this section are derived from study data and post-marketing experience of ONIVYDE. The adverse reactions that may occur during treatment with ONIVYDE are summarised below and are presented by system organ class and frequency category (Table 3). Within

each system organ class and frequency category, adverse reactions are presented in order of decreasing seriousness. Frequencies categories used for adverse reactions are: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) * and not known (cannot be estimated from the available data).

Table 3: Adverse reactions reported with ONIVYDE therapy in NAPOLI-1

MedDRA* Standard System Organ Class	**Adverse reaction MedDRA* Preferred Term**	**Frequency****
Infections and infestations	Oral Candidiasis	Common
	Febrile Neutropenia	Common
	Gastroenteritis	Common
	Pneumonia	Common
	Device related infection	Common
	Sepsis	Common
	Septic shock	Common
	Biliary Sepsis	Uncommon
Blood and lymphatic system disorders	Neutropenia	Very common
	Leukopenia	Very common
	Anaemia	Very common
	Thrombocytopenia	Very common
	Lymphopenia	Common
Immune system disorders	Hypersensitivity	Uncommon
	Anaphylactic reaction	Not known**
	Anaphylactoid reaction	Not known**
	Angioedema	Not known**
Metabolism and nutrition disorders	Decreased appetite	Very common
	Hypokalemia	Very common
	Hypomagnesemia	Very common
	Dehydration	Very common
	Hypophosphatemia	Common
	Hyponatremia	Common
	Hypoglycemia	Common
Psychiatric disorders	Insomnia	Common
Nervous system disorders	Dizziness	Very common
	Dysgeusia	Common
	Cholinergic syndrome	Common
Cardiac disorders	Hypotension	Common
Vascular disorders	Deep vein thrombosis	Common
	Pulmonary embolism	Common
	Embolism	Common
	Thrombosis	Uncommon
Respiratory, thoracic & mediastinal disorders	Dysphonia	Common
	Dyspnoea	Common
	Hypoxia	Uncommon
Gastrointestinal disorders	Diarrhoea	Very common
	Vomiting	Very common

	Nausea	Very common
	Abdominal pain	Very common
	Stomatitis	Very common
	Colitis	Common
	Haemorrhoids	Common
	Oesophagitis	Uncommon
	Proctitis	Uncommon
	Hypoalbuminemia	Common
Skin & subcutaneous tissue disorders	Alopecia	Very common
	Rash maculo-papular	Uncommon
	Nail discolouration	Uncommon
	Erythema	Not known**
	Pruritus	Common***
	Rash	Uncommon***
	Urticaria	Uncommon***
Renal and urinary disorders	Acute kidney injury	Common
General disorders and administration site conditions	Fatigue	Very common
	Pyrexia	Very common
	Asthenia	Very common
	Mucosal inflammation	Very common
	Peripheral oedema	Very common
	Infusion related reaction	Common
	Oedema	Common
Investigations	Weight decrease	Very common
	Increased international normalized ratio	Common
	Increased alanine aminotransferase	Common
	Increased aspartate aminotransferase	Common
	Increased bilirubin	Common

* Rare occurrence cannot be estimated from the NAPOLI-1study due to the small sample size
** Post-marketing adverse reaction – frequency cannot be estimated from the available data
*** Post-marketing adverse reaction – frequency from NAPOLI-1 study assigned

Post-marketing surveillance
The most frequently reported events are diarrhoea, infusion reactions, vomiting, nausea, abdominal pain, fatigue, and neutropenia.

Description of selected adverse reactions

Myelosuppression
Myelosuppression (leukopenia, neutropenia, anemia and thrombocytopenia) was more common in the ONIVYDE + 5FU/LV arm compared to the 5-FU/LV control arm. Neutropenic fever/sepsis was infrequent, but appeared more frequently in the ONIVYDE + 5-FU/LV combination arm: in 4 patients (3.4%) and in 1 patient (0.7%) in the 5 FU/LV control arm.

Leukopenia/Neutropenia
Leukopenia/neutropenia were the most notable important haematological toxicities.

Grade 3+ neutropenia occurred in 27% (N = 117) of patients treated with ONIVYDE + 5-FU/LV (Caucasians: 18%, N = 73, Asians: 55%, N = 33), respectively, and in 1.5% (N = 134) of patients treated with 5-FU/LV.

Anaemia
Grade 3+ anaemia occurred in 10% (N = 117) of patients treated with ONIVYDE + 5-FU/LV, respectively, and in 7% (N = 134) of patients treated with 5-FU/LV.Thrombocytopenia
Grade 3+ thrombocytopenia occurred in in 2.6% (N = 117) of patients treated with ONIVYDE + 5-FU/LV and none (0%) in patients treated with 5-FU/LV.

Acute renal failure
Renal impairment and acute renal failure have been identified, usually in patients who become volume depleted from nausea/vomiting and/or diarrhoea. Acute renal failure was reported in 6 of 117 patients (5.1%) in the ONIVYDE+5-FU/LV arm, 10 of 147 (6.8%) in the ONIVYDE monotherapy arm and 6 of 134 patients (4.5%) in the 5-FU/LV arm.

Diarrhoea and related adverse reactions
Diarrhoea is a very common ADR leading to colitis, ileus, gastroenteritis, fatigue, dehydration, weight loss, renal toxicities, hyponatraemia, hypokalaemia. Renal impairment and acute renal failure have been identified, usually in patients who became volume depleted from severe vomiting and/or diarrhoea. In the clinical study evaluating ONIVYDE in combination with 5-fluorouracil and leucovorin in patients with metastatic pancreatic cancer, Grade 3 or Grade 4 diarrhea occurred in 15 out of 117 patients (13%) receiving ONIVYDE in combination with 5-fluorouracil and leucovorin (Caucasians: 22%, N = 73, Asians: 3%, N = 33). For patients experiencing late diarrhoea, the median time to late diarrhoea onset was 8 days from the previous dose of ONIVYDE.

Early onset diarrhoea, typically appearing ≤24 hours after dose administration, can occur but is infrequent and usually transient. Early onset diarrhoea may also be accompanied by cholinergic symptoms that can include rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis and intestinal hyperperistalsis that can induce abdominal cramping. In the clinical study evaluating ONIVYDE in combination with 5-fluorouracil and leucovorin, early diarrhea onset (within 1 day of ONIVYDE administration) occurred in 35 patients (30%) and cholinergic events occurred in 4 patients (3.4%) receiving ONIVYDE in combination with 5-fluorouracil and leucovorin.

Infusion reaction
Acute infusion reaction was reported in 8 of 117 patients (6.8%) in the ONIVYDE + 5-FU/LV arm, 3 of 147 patients (2.0%) in the ONIVYDE monotherapy arm, and 8 of 134 patients (6.0%) in the 5-FU/LV arm.

Other Special Populations

Asian population
Compared to Caucasians, Asian patients were observed with a lower incidence of diarrhoea [14 (19.2%) out of 73 Caucasians had a ≥ Grade 3 diarrhoea, and 1 out of 33 (3.3%) Asians had a ≥ Grade 3 diarrhoea], but a higher incidence and higher severity of neutropenia. In patients receiving ONIVYDE+5 FU/LV, the incidence of ≥ Grade 3 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. This is consistent with the population pharmacokinetic analysis that showed a lower exposure to irinotecan and a higher exposure to its active metabolite SN 38 in Asians than in Caucasians.

Patients with prior Whipple procedure
In the clinical study evaluating ONIVYDE+5-FU/LV, patients with a prior Whipple procedure had a higher risk of serious infections following treatment with ONIVYDE+5-FU/LV [9 of 29 (30%)] compared to 11 of 88 (12.5%) patients with no prior Whipple procedure

Patients with homozygous UGT1A1 activity
Individuals who are 7/7 homozygous for the UGT1A1*28 allele are at increased risk for neutropenia from non-liposomal irinotecan. In the clinical study evaluating ONIVYDE in combination with 5-fluorouracil and leucovorin in patients with metastatic adenocarcinoma of pancreas, patients homozygous for the UGT1A1*28 allele did not experience a greater incidence of Grade 3 or Grade 4 neutropenia than those not homozygous (2 out of 7 patients (28.6%) versus 30 out of 110 patients (27.3%) respectively).

Underweight patients (body mass index < 18.5 kg/m2)
In the clinical study evaluating ONIVYDE+5-FU/LV, 5 of 8 underweight patients experienced grade 3 or higher adverse reaction, mostly myelosuppression, while 7 of the 8 patients required dose modification such as dose delay, dose reduction or dose discontinuation.

Pediatric population

No studies have been conducted in paediatric patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcareprofessionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

In clinical trials, ONIVYDE was administered at doses up to 240mg/m^2 to patients with various cancers. The adverse reactions in these patients were similar to those reported with the recommended dosage and regimen.

There have been reports of overdosage with non-liposomal irinotecan at doses up to approximately twice the recommended therapeutic dose of irinotecan, which may be fatal. The most significant adverse reactions reported were severe neutropenia and severe diarrhoea.

There is no known antidote for overdose of ONIVYDE. Maximum supportive care should be instituted to prevent dehydration due to diarrhoea and to treat any infectious complications.

For advice on the management of overdose please the National Poisons Centre at on phone number: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

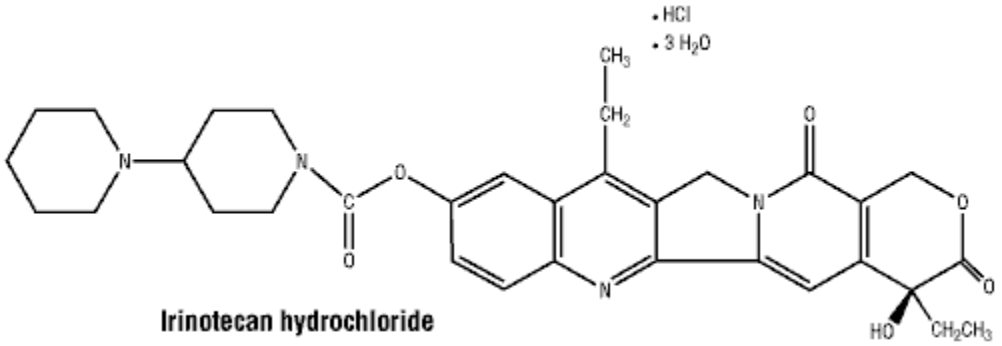
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, other antineoplastic agents, ATC code: L01XX19.

Chemical name: (4S)-4, 11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino) carbonyloxy]-1H-pyrano[3', 4':6, 7]indolizino[1, 2-b]quinoline-3, 14(4H, 12H) dione hydrochloride trihydrate

Structure:



Irinotecan hydrochloride

INN:	Irinotecan
CAS number:	136572-09-3
Molecular formula:	$C_{33}H_{38}N_4O_6.HCl.3H_2O$
Molecular weight:	677.19.*Mechanism of action*

The active ingredient in ONIVYDE is irinotecan which is encapsulated in long-circulating liposomes. The medicine product liposome is a small unilamellar lipid bilayer vesicle, approximately 110nm in diameter, which encapsulates an aqueous space which contains irinotecan in a gelated or precipitated state, as sucrosofate salt. ONIVYDE has been shown to extend circulation of irinotecan and prolong the duration of active therapy at the site of tumor cells to inhibit tumour growth.

Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I, which relieves torsional strain in DNA by inducing reversible single-strand breaks, rotating the cleaved strand around the double helix axis and re-ligating the cleaved strand to re-establish intact duplex DNA. Irinotecan and its active metabolite SN-38 bind reversibly to the topoisomerase I-DNA complex and prevent re-ligation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-38 is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumor cell lines.

Clinical trials

The efficacy of ONIVYDE was evaluated in NAPOLI-1, a three-arm, randomised, open label trial in 417 patients with metastatic pancreatic adenocarcinoma who had documented disease progression after gemcitabine-based therapy. Key eligibility criteria were Karnofsky Performance Status (KPS) ≥ 70, normal bilirubin level, transaminase levels ≤ 2.5 times the upper limit of normal (ULN) or ≤ 5 times the ULN for patients with liver metastasis and albumin ≥ 3.0g/dL. Patients were randomised to receive ONIVYDE plus 5-fluorouracil/ leucovorin (N = 117), ONIVYDE monotherapy (N = 151), or 5-fluorouracil/leucovorin (N = 149). Patients randomized to ONIVYDE plus 5-fluorouracil/leucovorin received ONIVYDE 70mg/m^2 as an intravenous infusion over 90 minutes, followed by leucovorin 400mg/m^2 intravenously over 30 minutes, followed by 5-fluorouracil 2400mg/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 expressed as irinotecan hydrochloride trihydrate).

Patients randomised to ONIVYDE monotherapy received 100mg/m^2 as an intravenous infusion over 90 minutes every 3 weeks. Patients randomized to 5- fluorouracil/leucovorin received leucovorin 200mg/m^2 intravenously over 30 minutes, followed by 5-fluorouracil 2000mg/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 treatment at a reduced dose (50mg/m^2 ONIVYDE plus 5-fluorouracil/leucovorin or 70mg/m^2 ONIVYDE monotherapy) (see section 4.2). Treatment continued until disease progression or unacceptable toxicity.

Patients enrolled in NAPOLI-1 had a median age of 63 years (range 31 - 87 years) with 46% ≥ 65 years of age; 57% were men; 61% were White and 33% were Asian. Mean baseline albumin level was 3.96g/dL, and baseline KPS was 90 - 100 in 55% of patients. Disease characteristics included 68% of patients with liver metastasis and 31% with lung metastasis; 12% of patients had no prior lines of metastatic therapy, 56% of patients had 1 prior line of metastatic therapy, 32% of patients had 2 or more prior lines of metastatic therapy. For the treated population, the median relative dose intensity for ONIVYDE was 88% in the ONIVYDE plus fluorouracil/leucovorin arm.

The major efficacy measure was overall survival (OS). Additional outcome measures included progression-free survival (PFS) and objective response rate (ORR). Assessments were conducted at baseline and every 6 weeks thereafter. Comparison of the ONIVYDE plus 5-fluorouracil/leucovorin arm to the 5-fluorouracil/leucovorin arm demonstrated improvement in overall survival and the other efficacy outcomes summarised in Table 4 and Figures 1. Comparison of the ONIVYDE monotherapy arm to the 5-fluorouracil/leucovorin control arm did not demonstrate evidence of an improvement in overall survival compared to the 5-fluorouracil/leucovorin control arm (hazard ratio = 0.99, logrank two-sided p-value = 0.9416).

Table 4 Efficacy Results from NAPOLI-1

	ONIVYDE + 5-FU/LV (N = 117)	**5-FU/LV (N = 119)**
Overall Survival*		
Number of Deaths, n (%)	75 (64)	80 (67)
Median Overall Survival (months)	6.1	4.2
(95% CI)	(4.8, 8.9)	(3.3, 5.3)
Hazard Ratio (95% CI)[§]	0.67 (0.49 – 0.92)	
p-value[¶]	0.0122	
Progression-Free Survival*,[†]		
Death or Progression, n (%)	83 (71)	92 (77)
Median Progression-Free Survival (months)	3.1	1.5
(95% CI)	(2.7, 4.2)	(1.4, 1.8)
Hazard Ratio (95% CI)§	0.56 (0.41 – 0.75)	
p-value[¶]	0.0001	
Objective Response Rate[†]		
Responder, n	19	1
Rate (%)	16.2	0.8
95% CI of Rate[#]	9.6, 22.9	0.0, 2.5
p-value♠	< 0.0001	
Tumour Marker CA 19-9 Response^		
n/N (%)	28/97 (28.9)	7/81 (8.6)
p-Value[¶]	0.0006	

* Median is the Kaplan-Meier estimate of the median survival time § Cox model analysis # Based on Normal approximation † Per RECIST guidelines,v1.1 ¶ Unstratified log-rank test ♠ Fisher's exact test ^Evaluable population defined as patients who received treatment and had baseline CA 19-9 >30 U/mL. Tumour marker response is achievement of 50% decrease in CA 19-9 relative to baseline value Abbreviations: 5-FU/LV = 5-fluorouracil/leucovorin; CI = confidence interval; PFS = progression free survival; HR = hazard ratio of ONIVYDE + 5-FU/LV compared with 5-FU/LV

Figure 1: Overall Survival from the NAPOLI-1 Study

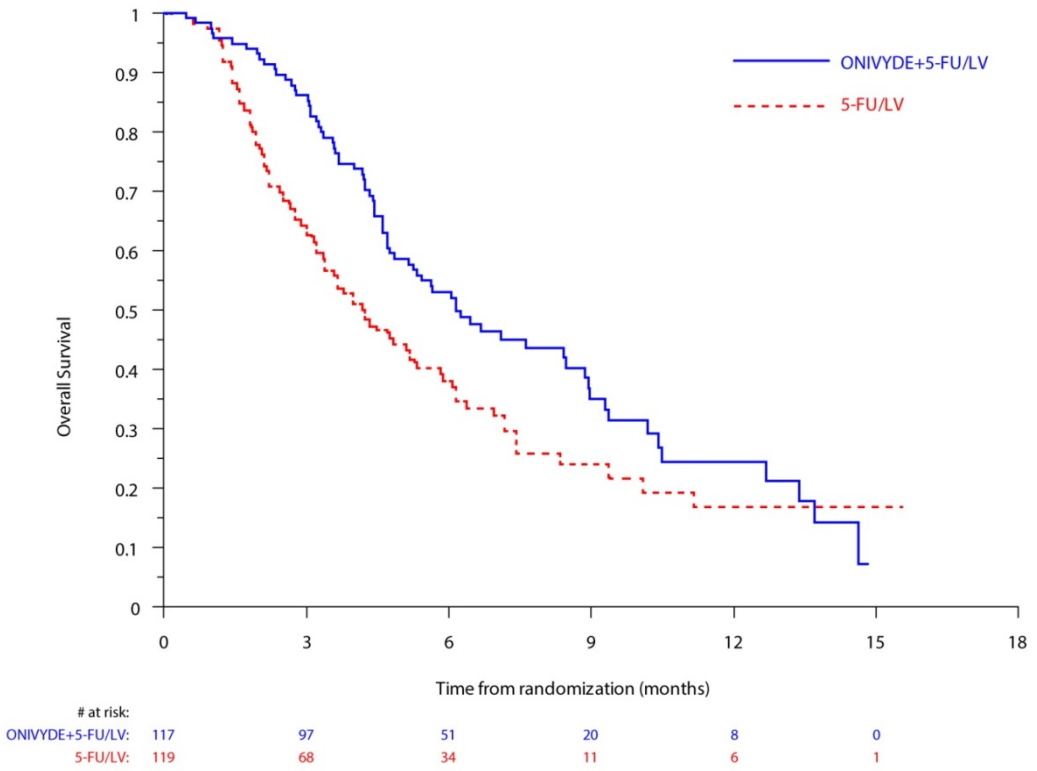


Figure 1: Overall Survival

A treatment effect on overall survival was consistently observed with ONIVYDE plus 5-fluorouracil/leucovorin in prospective analyses of stratification factor subgroups with a sufficient number of subjects.

5.2 Pharmacokinetic properties

Absorption

Liposome encapsulation can substantially affect a medicine's functional properties relative to those of the non-liposomal drug substance.

The plasma pharmacokinetics of ONIVYDE was evaluated from pooled data of 95 patients with solid tumours. Patients received ONIVYDE as monotherapy or as part of combination therapy at doses between 50 to 155mg/m^2. The pharmacokinetic parameters of total (both in liposome and free) irinotecan and SN-38, following the administration of ONIVYDE at 70mg/m^2 are presented in Table 5.

Table 5 Summary of Median (%IQR) Total Irinotecan and SN-38 Pharmacokinetic Parameters in Patients with Solid Tumors

	Total Irinotecan				**SN-38**		
Dose (mg/m^2)	**C (µg/mL) n = 25**	**$t_{1/2}$ (h) n = 23**	**$AUC_{0-\infty}$ (h.µg/mL) n = 23**	**V_d (L/m^2) n = 23**	**C_{max} (ng/mL) n = 25**	**$t_{1/2}$ (h) n = 13**	**$AUC_{0-\infty}$ (h.ng/mL) n = 13**
70	38.0 (36%)	26.8 (110%)	1030 (169%)	2.2 (55%)	4.7 (89%)	49.3 (103%)	587 (69%)

%IQR: % Interquartile Ratio = Interquartile – range/median*100%
$t_{1/2}$, $AUC_{0-\infty}$ and V_d were only calculated for a subset of patients with sufficient number of samples in the terminal phase
C_{max}: Maximum plasma concentration
$t_{1/2}$: Terminal half-life
$AUC_{0-\infty}$: Area under the plasma concentration curve extrapolated to time infinity
V_d: Volume of distribution

Over the dose range of 50 to 155 mg/m^2, the maximum total concentration of both irinotecan and SN-38 increased linearly with dose. The AUC of total irinotecan increased linearly with dose; the AUC of SN-38 increased less than proportionally with dose. The half-lives of both total irinotecan and SN-38 do not change with dose.

In a pooled analysis from 353 patients, higher plasma SN-38 C_{max} was associated with increased likelihood of experiencing neutropenia, and higher plasma total irinotecan C_{max} was associated with increased likelihood of experiencing diarrhoea.

In the clinical trial demonstrating effectiveness of ONIVYDE, higher plasma exposures of total irinotecan and SN-38 for patients in the ONIVYDE + 5FU/LV treatment arm were associated with longer OS and PFS (and lower hazard ratios) and higher ORR.

Distribution

Direct measurement of liposomal irinotecan shows that 95% of irinotecan remains liposome-encapsulated during circulation. Non-liposomal irinotecan displays a large volume of distribution (range: 110-234L/m^2). The volume of distribution of ONIVYDE 70mg/m^2 was 2.2L/m^2, which suggests that ONIVYDE is largely confined to vascular fluid.

The plasma protein binding of ONIVYDE is negligible (< 0.44% of total irinotecan in ONIVYDE). The plasma protein binding of non-liposomal irinotecan is moderate (30% to 68%) and SN-38 is highly bound to human plasma proteins (approximately 95%).

Metabolism

ONIVYDE follows the metabolic fate of irinotecan.

The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes. *In vitro* studies indicate that irinotecan, SN-38 and another metabolite aminopentane carboxylic acid (APC), do not inhibit cytochrome P-450 isozymes. SN-38 is subsequently conjugated predominantly by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite. UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Based on the results of the population PK analysis, patients homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) had similar SN-38 exposure.

Excretion

The disposition of ONIVYDE and non-liposomal irinotecan has not been fully elucidated in humans. The urinary excretion of non-liposomal 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 in two patients ranged from approximately 25% (100mg/m^2) to 50% (300mg/m^2).

A mass balance study in Sprague-Dawley rats, using liposomal encapsulated 14C-irinotecan, showed that once irinotecan was released from the liposomes, it followed the same elimination pathway as unencapsulated irinotecan. Faecal excretion was the major route of excretion in male and female rats, accounting for 78.3% and 83.4% respectively of the total radioactivity dose administered of liposomal encapsulated 14C-irinotecan over 168 hours.

5.3 Preclinical safety data

In single and repeated dose toxicity studies in mice, rats and dogs, the target organs of toxicity were the gastrointestinal tract and the hematologic system. The severity of effects was dose-related and reversible. The no-observed-adverse-effect level (NOAEL) in rats and dogs following 90 min intravenous infusion of ONIVYDE once every 3 weeks for 18 weeks was at least 156 mg/m^2. In safety pharmacology studies in dogs, ONIVYDE had no effect on cardiovascular, hemodynamic, electrocardiographic, or respiratory parameters at doses up to 18 mg/kg (364 mg/m^2). No findings indicative of CNS related toxicity were observed in the repeated dose toxicity studies in rats.

Genotoxic and carcinogenic potential

No genotoxicity studies have been performed with ONIVYDE. Non-liposomal irinotecan and SN-38 were genotoxic *in vitro* in the chromosomal aberration test on CHO-cells as well as in the *in vivo* micronucleus test in mice. However, in other studies with irinotecan they have been shown to be devoid of any mutagenic potential in the Ames test.

No carcinogenicity studies have been performed with ONIVYDE. For non-liposomal irinotecan, in rats treated once a week during 13 weeks at the maximum dose of 130 mg/m^2, no treatment related tumours were reported 91 weeks after the end of treatment. Under these conditions, there was a significant linear trend with dose for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas. Due to its mechanism of action, irinotecan is considered a potential carcinogen.

Reproduction toxicity

No reproductive and developmental toxicity studies have been performed with ONIVYDE. Non-liposomal irinotecan was teratogenic in rats and rabbits at doses below the human therapeutic dose. In rats, pups born from treated animals and having external abnormalities showed a decrease in fertility. This was not seen in morphologically normal pups. In pregnant rats there was a decrease in placental weight and in the offspring a decrease in foetal viability and increase in behavioural abnormalities.

Non-liposomal irinotecan caused atrophy of male reproductive organs both in rats and dogs after multiple daily doses of 17mg/kg and 0.3 mg/kg, respectively. These effects were reversible upon cessation of treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liposome forming lipids
Cholesterol
1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
[N-(carbonylmethoxypolyethyleneglycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine] (MPEG-2000-DSPE)

Other excipients
2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid (HEPES)
Sucrose octasulfate
Sodium chloride
Water for injection

6.2 Incompatibilities

ONIVYDE must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
36 months

Diluted
6 hours diluted stored at or below 25°C protect from light. Do not freeze.
24 hours diluted stored at 2° to 8°C. Refrigerate, do not freeze, protect from light.

Contains no antimicrobial preservative.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Protect from light.

For storage conditions after dilution of medicinal product, see section 6.3.

6.5 Nature and contents of container

10 mL vial (type I glass) with a 20mm, grey chlorobutyl stopper and a 20mm aluminium seal with a flip-off cap, containing irinotecan sucrosofate equivalent to 43 mg irinotecan or 50mg irinotecan

hydrochloride trihydrate in the form of the sucrosofate salt, encapsulated in liposomes, as a dispersion.

Each pack contains one vial

6.6 Special precautions for disposal

ONIVYDE is for single use in one patient only.

ONIVYDE is a cytotoxic medicine and caution should be exercised in handling it. The use of gloves, goggles, and protective clothing when handling or administering ONIVYDE is recommended. If the solution contacts the skin, the skin should be washed immediately and thoroughly with soap and water. If the solution contacts mucous membranes, they should be flushed thoroughly with water. Pregnant staff should not handle ONIVYDE considering the cytotoxic nature of the agent.

Preparation of the solution and administration
ONIVYDE is supplied as a sterile liposomal dispersion at a concentration of 4.3 mg/mL and must be diluted prior to administration. Dilute with 5%w/v glucose solution for injection or 0.9% sodium chloride solution for injection to prepare a solution of the appropriate dose of ONIVYDE diluted to a final volume of 500 mL. Mix diluted solution by gentle inversion.

ONIVYDE should be administered before LV followed by 5-FU. ONIVYDE must not be administered as a bolus injection or an undiluted solution.

Aseptic techniques must be followed during the preparation of the infusion. ONIVYDE is for single use only.

From a microbiological point of view, the product should be used as soon as possible after dilution, but may be stored at ambient temperature for up to 6 hours. The diluted solution for infusion can be stored in the refrigerator (2ºC to 8ºC) for no more than 24 hours prior to use. Protect diluted solution from light. Do not freeze diluted solution.

Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with normal saline and/or sterile water and applications of ice are recommended.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Only Medicine.

8 SPONSOR

Distributed in New Zealand by:

Servier Laboratories (NZ) Limited
Level 4, Zurich House
21 Queen Street
Auckland Central
Auckland 1010

9 DATE OF FIRST APPROVAL

20 September 2018

10 DATE OF REVISION OF THE TEXT

30 Jan 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4, 4.4, 4.5, 4.6 4.8, 4.9, 5.1 5.2, 6.5, 6.6, 8	To Align with TGA approved PI (Aligned with Datasheet)
4.2, 4.4	Safety-related update to sections 4.4 and 4.6.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.

ONIVYDE® is a registered trademark of Ipsen Bioscience Inc. and is used under license.