AUSTRALIAN PRODUCT INFORMATION

ONIVYDE® (NANOLIPOSOMAL IRINOTECAN AS SUCROSOFATE)

ONIVYDE is not equivalent to non-liposomal irinotecan hydrochloride and they should not be interchanged.

1 NAME OF THE MEDICINE

Nanoliposomal irinotecan as sucrosofate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ONIVYDE is a topoisomerase 1 inhibitor (irinotecan) encapsulated in lipid bilayer vesicles or liposomes, presented in solution as a liposomal dispersion for intravenous use. The liposome is a small unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, which encapsulates an aqueous space containing irinotecan in a gelated or precipitated state, as the sucrosofate (sucrose octasulfate) salt.

Each 10 mL vial contains 43 mg irinotecan (4.3 mg/mL) equivalent to 50 mg irinotecan hydrochloride trihydrate (5.0 mg/mL).

The liposome carriers are composed of 68.1 mg distearoylphosphatidylcholine (6.81 mg/mL); 22.2 mg cholesterol (2.22 mg/mL) and 1.2 mg Sodium methoxy PEG-40-carbonyl-distearoylphosphatidylethanolamine (0.12 mg/mL). The solution is buffered at pH 7.25.

For the full list of excipients, see *section 6.1 - List of excipients*.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ONIVYDE is indicated:

- in combination with oxaliplatin and 5-fluorouracil (5-FU) and leucovorin (LV) for the first-line treatment of metastatic pancreatic adenocarcinoma.
- in combination with 5-FU and LV for the treatment of metastatic pancreatic adenocarcinoma after disease progression following 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.

FOR INTRAVENOUS USE ONLY.

Dosage

First-line treatment of metastatic pancreatic adenocarcinoma

ONIVYDE, oxaliplatin, LV and 5-FU (also known collectively as NALIRIFOX) should be administered sequentially. The recommended dose and regimen of ONIVYDE (regardless of UGT1A1 genomic status) is 50 mg/m² intravenously over 90 minutes, followed by oxaliplatin 60 mg/m^2 intravenously over 120 minutes, followed by LV 400 mg/m^2 intravenously over 30 minutes, followed by 5-FU 2,400 mg/m^2 intravenously over 46 hours, administered every 2 weeks until development of disease progression or unacceptable toxicity.

Treatment of metastatic pancreatic adenocarcinoma after prior gemcitabine-based therapy

ONIVYDE, LV and 5-FU should be administered sequentially. The recommended dose and regimen of ONIVYDE is 70 mg/m^2 intravenously over 90 minutes, followed by LV 400 mg/m^2 intravenously over 30 minutes, followed by 5-FU 2,400 mg/m^2 intravenously over 46 hours, administered every 2 weeks until development of disease progression or unacceptable toxicity. For patients known to be homozygous for the UGT1A1*28 allele, consider a reduced ONIVYDE starting dose of 50 mg/m^2, with an increase to 70 mg/m^2 as tolerated in subsequent cycles (see *section 5.1 – Pharmacodynamic properties – Clinical Trials* and *section 5.2 – Pharmacokinetic properties*).

Premedication

Administer a corticosteroid and an antiemetic 30 minutes prior to each ONIVYDE infusion.

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 using aseptic technique prior to administration.

Withdraw the appropriate volume of concentrate containing the required dose of ONIVYDE from the vial, and dilute to a final volume of 500 mL using either 5% w/v glucose solution for injection or 0.9% sodium chloride solution for injection. Mix diluted solution by gentle inversion.

ONIVYDE is for single use only - discard vials with any unused portion.

Use the diluted ONIVYDE solution as possible after dilution to minimise microbiological risk. Administer within 6 hours of dilution if stored at ambient temperature, or within 24 hours if stored in a refrigerator (2°C to 8°C). Allow diluted solution to come to room temperature prior to administration. Protect the diluted solution from light, and do not freeze it.

Infuse the diluted ONIVYDE solution intravenously over at least 90 minutes, through a 21 gauge (or smaller) needle. Do not use any in-line filters.

Take care to avoid extravasation and monitor the infusion site for signs of inflammation. Should extravasation occur, flush the site with normal saline and/or sterile water and apply ice.

Dose modifications

First-line treatment of metastatic pancreatic adenocarcinoma

Recommended dose modifications for ONIVYDE in combination with oxaliplatin and 5-FU and LV (NALIRIFOX regimen) in case of toxicity are summarised in Table 1.

Table 1: Recommended dose modifications for ONIVYDE in combination with oxaliplatin and 5-FU and LV (NALIRIFOX regimen)

<table>
<tr><th>Toxicity [a]</th><th>Occurrence</th><th colspan="2">ONIVYDE/oxaliplatin/5-FU/LV (NALIRIFOX) modifications</th></tr>
<tr><td>Grade 3 or 4 palmar-plantar erythrodysaesthesia</td><td rowspan="5">First</td><td colspan="2" rowspan="5">Discontinue treatment</td></tr>
<tr><td>Any grade neurocerebellar toxicity</td></tr>
<tr><td>≥Grade 2 cardiac toxicity</td></tr>
<tr><td>Anaphylactic reaction</td></tr>
<tr><td>Interstitial lung disease / pneumonitis</td></tr>
<tr><td rowspan="4">Other Grade 3 or 4 toxicities [b c]</td><td>First</td><td rowspan="3">Withhold treatment until toxicity recovers to ≤ Grade 1 [d]</td><td>Resume ONIVYDE, oxaliplatin and 5-FU each at 80% of initial dose [e]</td></tr>
<tr><td>Second</td><td>Resume ONIVYDE, oxaliplatin and 5-FU each at 65% of initial dose [e]</td></tr>
<tr><td>Third</td><td>Resume ONIVYDE, oxaliplatin and 5-FU each at 50% of initial dose [e]</td></tr>
<tr><td>Fourth</td><td colspan="2">Discontinue treatment</td></tr>
<tr><td colspan="4">[a] Toxicity grades according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.
[b] No dose modification is required for asthenia, alopecia, or Grade 3 anorexia.
[c] Modify dose for Grade ≥3 nausea and vomiting only if it occurs despite optimal antiemetic therapy
[d] Do not resume until the absolute neutrophil count is ≥2000 cells/mm^3 (2x10^9/L) and the platelet count is ≥100,000 cells/mm^3 (100x10^9/L).
[e] Refer to the Product Information of fluorouracil and oxaliplatin for further information. Oxaliplatin may be discontinued if not well tolerated and treatment with ONIVYDE + 5-FU + LV can continue. Maintain original dose of leucovorin for first, second and third occurrence of toxicity. Dose reductions are the same regardless of UGT1A1 genomic status.</td></tr>
</table>

Treatment of metastatic pancreatic adenocarcinoma after prior gemcitabine-based therapy

Recommended dose modifications for ONIVYDE in combination with 5-FU and LV in case of toxicity are summarised in Table 2.

Table 2: Recommended dose modifications for ONIVYDE in combination with 5-FU and LV (ONIVYDE+5-FU/LV)

<table>
<tr><th>Toxicity [a]</th><th>Occurrence</th><th colspan="2">ONIVYDE+5-FU/LV modifications</th></tr>
<tr><td>Anaphylactic reaction</td><td rowspan="2">First</td><td colspan="2" rowspan="2">Discontinue treatment</td></tr>
<tr><td>Interstitial lung disease / pneumonitis</td></tr>
<tr><td rowspan="3">Other Grade 3 or 4 toxicities [b c]</td><td>First</td><td rowspan="2">Withhold treatment until toxicity recovers to ≤ Grade 1 [d]</td><td>Resume ONIVYDE at 50 mg/m^2 [e] and 5-FU at 1,800 mg/m^2 [f]</td></tr>
<tr><td>Second</td><td>Resume ONIVYDE at 43 mg/m^2 [g] and 5-FU at 1,350 mg/m^2 [f]</td></tr>
<tr><td>Third</td><td colspan="2">Discontinue treatment</td></tr>
</table>

Toxicity [a]	Occurrence	ONIVYDE+5-FU/LV modifications
[a] Toxicity grades according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. [b] No dose modification is required for asthenia, alopecia, or grade 3 anorexia. [c] Modify dose for Grade ≥3 nausea and vomiting only if it occurs despite optimal antiemetic therapy [d] Do not resume until the absolute neutrophil count is ≥1500 cells/mm^3 ($1.5x10^9$/L) and the platelet count is ≥100,000 cells/mm^3 ($100x10^9$/L). [e] For patients homozygous for UGT1A1*28 who were on ONIVYDE 50 mg/m^2 when first toxicity occurred, recommence ONIVYDE at 43 mg/m^2 after recovery. [f] Refer to the Product Information of fluorouracil for further information. Maintain original dose of leucovorin for first and second occurrence of toxicity. [g] For patients homozygous for UGT1A1*28 who were on ONIVYDE 43 mg/m^2 at time of second toxicity, recommence ONIVYDE at 35 mg/m^2 after recovery.		

Patients with hepatic impairment

No dedicated hepatic impairment study has been conducted with ONIVYDE. Patients with hyperbilirubinaemia had higher concentrations for total SN-38 (see *section 5.2 - Pharmacokinetic properties*) and therefore the risk of neutropenia is increased. Frequent monitoring of complete blood counts should be conducted in this patient population. The use of ONIVYDE should be avoided in patients with bilirubin >34 µmol/L or aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >2.5 times upper limit of normal (ULN) or >5 times ULN if liver metastasis is present, see *section 4.4 - Special warnings and precautions for use*.

4.3 CONTRAINDICATIONS

ONIVYDE is contraindicated in patients with hypersensitivity to irinotecan or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Interchangeability of formulation

ONIVYDE is a liposome-encapsulated formulation of irinotecan (sucrosofate) with different pharmacokinetics and dosing to non-liposomal irinotecan (hydrochloride). They should not be interchanged.

Myelosuppression/neutropenia

Myelosuppression with severe neutropenia is very common with ONIVYDE treatment, and life-threatening neutropenic sepsis (with or without a febrile response, i.e. febrile neutropenia) can occur.

In NAPOLI 3, Grade 3 and 4 neutropenia occurred in 26% of patients receiving ONIVYDE in combination with oxaliplatin, fluorouracil, and leucovorin (NALIRIFOX) and fatal neutropenic sepsis occurred in 0.3% of patients. In NAPOLI-1, Grade 3 and 4 neutropenia occurred in 20% of patients receiving ONIVYDE in combination with fluorouracil and leucovorin (ONIVYDE/FU/LV). Neutropenic sepsis occurred in 3% and fatal neutropenic sepsis in 0.8% (see *section 4.8 – Adverse effects (undesirable effects)*).

Inform patients of the significance of fever. Assess full blood cell counts on Days 1 and 8 of every cycle and more frequently if clinically indicated. For patients at higher risk of severe myelosuppression (such as those with a history of abdominal radiation), monitor closely, and consider myeloid growth factors. Use

concurrent ONIVYDE and irradiation with caution. Patients with severe bone marrow failure should not receive ONIVYDE.

Withhold ONIVYDE for absolute neutrophil count below 1.5 x 10^9/L, any occurrence of febrile neutropenia, or platelet count below 100 x 10^9/L. Febrile neutropenia (body temperature >38°C and neutrophil count <1.0 x 10^9/L) should be urgently treated in the hospital with broad-spectrum intravenous antibiotics. After recovery, depending on severity and number of recurrences of haematological events, resume at a reduced dose or discontinue (see *section 4.2 – Dose and method of administration – Dose modifications).*

Severe diarrhoea

Severe diarrhoea is very common with ONIVYDE treatment, and can have life-threatening sequelae such as dehydration, electrolyte imbalances, renal toxicity, inflammation and infection. Renal impairment and fatal acute renal failure have occurred (see *section 4.8 – Adverse effects (Undesirable effects)*. ONIVYDE must not be administered to patients with bowel obstruction or chronic inflammatory bowel disease.

Diarrhoea can occur early (onset within 24 hours of starting ONIVYDE) or late. Early diarrhoea is usually transient and may be accompanied by other cholinergic symptoms (see below). An individual patient may experience both early and late diarrhoea.

In NAPOLI 3, Grade 3 and 4 diarrhoea (early or late-onset) occurred in 20% of patients receiving ONIVYDE (as part of the NALIRIFOX regimen). In NAPOLI-1, Grade 3 or 4 diarrhoea occurred in 13% of patients receiving ONIVYDE (in combination with 5-FU/LV): 9% experienced late-onset and 3% experienced early-onset diarrhoea. Of patients receiving ONIVYDE+5-FU/LV in NAPOLI-1, 34% received loperamide for late-onset diarrhoea and 26% received atropine for early-onset diarrhea.

Inform patients of the potential for life-threatening sequelae, and the importance of immediate treatment at first sign of loose or frequent stools. To help avoid severe diarrhoea, patients should stop lactose-containing products, eat a low-fat diet and maintain hydration during treatment with ONIVYDE.

Withhold ONIVYDE for all Grade ≥2 diarrhoea. For early-onset diarrhoea of any severity, administer atropine (0.25 to 1 mg, intravenous or subcutaneous) unless contraindicated, and consider atropine prophylaxis. For late-onset diarrhoea of any severity, initiate loperamide (maximum cumulative daily dose 16 mg). Ensure patients have loperamide readily available to begin treatment as soon as symptoms are noticed. Cease loperamide when diarrhoea has not recurred for at least 12 consecutive hours, or if diarrhoea persists at 48 hours. Local institutional guidelines should be followed for the treatment of diarrhoea that does not improve with loperamide treatment within 24 to 48 hours, including monitoring and replacing fluid and electrolytes, consideration of antibiotic support (e.g. 7 days of oral fluoroquinolone) and potentially the use of diphenoxylate hydrochloride plus atropine sulfate or octreotide. After recovery, depending on severity and number of recurrences of diarrhoea, resume at a reduced dose or discontinue (see *section 4.2 - Dose and method of administration – Dose modifications)*).

Cholinergic reactions

ONIVYDE can cause cholinergic reactions manifesting as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis, and intestinal hyperperistalsis with abdominal cramping and early-onset diarrhoea. Treat with atropine, as described above (for early-onset diarrhoea).

Based on experience with non-liposomal irinotecan in patients with asthma, cardiovascular diseases or urinary obstruction, ONIVYDE should be used with caution in these patients.

Hypersensitivity and infusion-related reactions

ONIVYDE can cause acute infusion reactions (including rash, urticaria, periorbital oedema or pruritus), and anaphylactic/anaphylactoid reactions and angioedema may occur. ONIVYDE should be discontinued in case of severe hypersensitivity reactions (see *section 4.2 – Dose and method of administration*).

Interstitial lung disease/pneumonitis

Non-liposomal irinotecan (hydrochloride) can cause severe or fatal interstitial lung disease (ILD)/pneumonitis. Pneumonitis was reported in 0.3% of patients receiving ONIVYDE in combination with oxaliplatin and 5-FU/LV (NALIRIFOX) in NAPOLI-3. Risk factors include pre-existing lung disease, use of pneumotoxic medicinal products, colony stimulating factors or having previously received radiation therapy. Patients with risk factors should be closely monitored for respiratory symptoms before and during ONIVYDE therapy. New or progressive dyspnoea, cough, and fever should prompt interruption of ONIVYDE treatment, pending diagnostic evaluation. ONIVYDE should be discontinued in patients with a confirmed diagnosis of ILD.

Immunosuppression and live vaccines

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents, including ONIVYDE, may result in serious or fatal infections. Live vaccines should be avoided in patients receiving ONIVYDE. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Thromboembolism

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.

Poor performance status

ONIVYDE has not been studied in patients with a Karnofsky performance status (KPS) score of <70 (see *section 5.1 - Pharmacodynamic properties - Clinical Trials).*

Use in hepatic impairment

Hyperbilirubinaemia is associated with lower SN-38 clearance, and higher risk of neutropenia (see *section 4.8 – Adverse effects (undesirable effects) – Safety in specific populations* and *section 5.2 Pharmacokinetic properties*). No dedicated hepatic impairment study has been conducted with ONIVYDE, and patients with elevated baseline serum bilirubin were excluded from ONIVYDE clinical trials.

Monitor blood counts regularly in patients with total bilirubin of 1.0-2.0 mg/dL. Use cautiously in patients with hepatic impairment (bilirubin >2 times the upper limit of normal [ULN]; transaminases >5 times ULN), with deficiency of bilirubin glucuronidation (such as Gilbert's syndrome), and those taking other hepatotoxic substances.

Use in renal impairment

No dedicated pharmacokinetic study has been conducted in patients with renal impairment. Creatinine clearance was not found as a significant covariate on SN-38 clearance. There was insufficient data in patients with severe renal impairment (CLcr < 30 mL/min) to assess its effect on pharmacokinetics.

Use in the elderly

Meaningful differences in clinical safety and efficacy were not detected in subgroup analyses based on age above or below 65 years (see *section 4.8 – Adverse effects (undesirable effects) – Safety in particular populations*).

Paediatric use

The safety and efficacy of ONIVYDE in patients under the age of 18 years has not been established.

Effects on laboratory tests

See *section 4.8 Adverse effects (undesirable effects) – Table 4 and Table 6.*

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interactions with combination partner drugs

In a population pharmacokinetic analysis, the pharmacokinetics of total irinotecan and total SN-38 were not altered by the co-administration of fluorouracil/leucovorin. In NAPOLI-3, irinotecan AUC decreased by 33% and SN-38 C_{max} increased by 23% following co-administration with oxaliplatin.

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, telaprevir, 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.

CYP substrates

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

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 ONIVYDE.

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-fluorouracil)

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

There are no clinical data on fertility. Effects of liposome encapsulated irinotecan on fertility have not been assessed in animal studies. Prior to starting the administration of ONIVYDE consider advising patients on the preservation of gametes.

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 active ingredient irinotecan has been shown to be embryotoxic and teratogenic in animals.

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Summary of the safety profile

The safety profile for ONIVYDE is based on adverse reactions data from two international, randomised, active-controlled, open-label studies (see also *section 5.1 Pharmacodynamic properties – Clinical trials*).

- NAPOLI-1 (a study of ONIVYDE as an add-on to 5-FU and LV [ONIVYDE+5-FU/LV] for the treatment of metastatic pancreatic adenocarcinoma after progression on prior gemcitabine-based therapy)
    - 117 patients in this study received ONIVYDE+5-FU/LV
    - 147 patients in this study received ONIVYDE as monotherapy (noting that the efficacy of ONIVYDE monotherapy has not been established)
- NAPOLI-3 (a study of ONIVYDE in combination with oxaliplatin and 5-FU and LV [NALIRIFOX] for the first-line treatment of metastatic pancreatic adenocarcinoma)
    - 370 patients in this study received ONIVYDE in the NALIRIFOX arm

In combination with fluorouracil and leucovorin for treatment of metastatic pancreatic adenocarcinoma after progression on gemcitabine or gemcitabine-based therapy (NAPOLI-1)

The safety data described below are derived from patients with metastatic pancreatic adenocarcinoma previously treated with gemcitabine-based therapy who received any part of protocol-specified therapy in NAPOLI-1, an international, randomised, active-controlled, open-label trial. Protocol-specified therapy consisted of ONIVYDE 70 mg/m^2 with leucovorin 400 mg/m^2 and fluorouracil 2,400 mg/m^2 over 46 hours every 2 weeks (ONIVYDE/FU/LV; N=117), ONIVYDE 100 mg/m^2 every 3 weeks (N=147), or leucovorin 200 mg/m^2 and fluorouracil 2,000 mg/m^2 over 24 hours weekly for 4 weeks followed by 2 week rest (FU/LV; N=134) (see *section 5.1 Pharmacodynamic properties – Clinical trials*). 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/FU/LV arm, 9 weeks in the ONIVYDE monotherapy arm, and 6 weeks in the FU/LV arm.

The most common adverse reactions (≥20%) of ONIVYDE were diarrhoea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common, severe laboratory abnormalities (≥10% Grade 3 or 4) were lymphopenia and neutropenia. The most common serious adverse reactions (≥2%) of ONIVYDE were diarrhoea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

Adverse reactions led to permanent discontinuation of ONIVYDE in 11% of patients receiving ONIVYDE/FU/LV; the most frequent adverse reactions resulting in discontinuation of ONIVYDE were diarrhoea, vomiting, and sepsis. Dose reductions of ONIVYDE for adverse reactions occurred in 33% of patients receiving ONIVYDE/FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhoea, nausea, and anaemia. ONIVYDE was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE/FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhoea, fatigue, vomiting, and thrombocytopenia.

Table 3 and Table 4 summarise the adverse reactions and laboratory abnormalities that were more common with addition of ONIVYDE to treatment.

Table 3: Adverse reactions with higher incidence (≥5% difference for Grades 1-4* or ≥2% difference for Grades 3 and 4) in the ONIVYDE/FU/LV arm than the FU/LV arm) in NAPOLI-1

Adverse Reaction	ONIVYDE/FU/LV N=117		FU/LV N=134	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal disorders				
Diarrhoea	59	13	26	4
Early diarrhoea[†]	30	3	15	0
Late diarrhoea[‡]	43	9	17	4
Vomiting	52	11	26	3
Nausea	51	8	34	4
Stomatitis[§]	32	4	12	1
Infections and infestations	38	17	15	10
Sepsis	4	3	2	1
Neutropenic fever/neutropenic sepsis[♠]	3	3	1	0
Gastroenteritis	3	3	0	0
Intravenous catheter-related infection	3	3	0	0
General disorders and administration site conditions				
Fatigue/asthenia	56	21	43	10
Pyrexia	23	2	11	1
Metabolism and nutrition disorders				
Decreased appetite	44	4	32	2
Weight loss	17	2	7	0
Dehydration	8	4	7	2
Skin and subcutaneous tissue disorders				
Alopecia	14	1	5	0

[*] NCI CTCAE v4.0
[†] Early diarrhoea: onset within 24 hours of ONIVYDE administration
[‡] Late diarrhoea: onset >1 day after ONIVYDE administration
[§] Includes stomatitis, aphthous stomatitis, mouth ulceration, mucosal inflammation.
[♠] Includes febrile neutropenia

Table 4: Laboratory abnormalities[*#] with higher incidence (≥5% difference) in the ONIVYDE/5-FU/LV arm than the FU/LV arm in NAPOLI-1

Laboratory abnormality	ONIVYDE/5-FU/LV N=117		5-FU/LV N=134	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Haematology				
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.

In combination with oxaliplatin, fluorouracil and leucovorin for first-line treatment of metastatic pancreatic adenocarcinoma (NAPOLI-3)

The safety of ONIVYDE in patients with metastatic pancreatic adenocarcinoma who had not previously received chemotherapy was evaluated in NAPOLI-3 (see *section 5.1 – Pharmacodynamic properties – Clinical Trials*). Patients received ONIVYDE 50 mg/m² in combination with oxaliplatin 60 mg/m², leucovorin 400 mg/m² and fluorouracil 2,400 mg/m² over 46 hours every 2 weeks (NALIRIFOX; N=383) or nab-paclitaxel 125 mg/m² over 35 minutes and gemcitabine 1,000 mg/m² over 30 minutes on Day 1, 8 and 15 of each 28-day cycle (Gem+NabP; N=387). The median duration of exposure to ONIVYDE in combination with oxaliplatin, fluorouracil, and leucovorin was 24 weeks (range: 0 to 101 weeks).

Serious adverse reactions occurred in 54% of patients who received ONIVYDE in combination with oxaliplatin, fluorouracil and leucovorin. Serious adverse reactions in ≥2% of patients included infections including COVID-19 (14%), diarrhoea (9%), vomiting (6%), nausea (4.9%), fatigue (3.8%), embolism (3.5%), gastrointestinal tract stenosis or obstruction (3.5%), haemorrhage (3%), abdominal pain (2.7%), cerebrovascular accident (2.7%), dehydration (2.7%), liver function test abnormalities (2.2%), and pyrexia (2.2%). Fatal adverse reactions occurred in 6% of patients who received ONIVYDE in combination with oxaliplatin, fluorouracil and leucovorin including cerebrovascular accident (1.1%), haemorrhage (0.5%), pneumonia (0.5%), sepsis (0.5%) and sudden death (0.5%).

Permanent discontinuation of ONIVYDE due to an adverse reaction occurred in 17% of patients. Adverse reactions which resulted in permanent discontinuation of ONIVYDE in ≥1% of patients included neutropenia, thrombocytopenia, diarrhoea, fatigue, infections and cerebrovascular accident.

Dosage reduction of ONIVYDE due to an adverse reaction occurred in 52% of patients. Adverse reactions which required dosage reduction in ≥1% of patients included anaemia, decreased appetite, diarrhoea, fatigue, febrile neutropenia, hypokalaemia, liver function test abnormalities, nausea, mucosal inflammation, neutropenia, peripheral neuropathy, vomiting, thrombocytopenia and weight decreased.

Dosage interruptions of ONIVYDE due to an adverse reaction occurred in 1.9% of patients. Adverse reactions which required dosage interruption in ≥0.5% of patients included hypersensitivity and infusion related reaction.

The most common adverse reactions (≥20% with a difference between arms of ≥5% for all grades or ≥2% for Grades 3 or 4 compared to Gem+NabP) of ONIVYDE in combination with oxaliplatin, fluorouracil, and leucovorin were diarrhoea, fatigue, nausea, vomiting, decreased appetite, abdominal pain, mucosal inflammation, constipation and decreased weight. The most common laboratory abnormalities (≥10% Grade 3 or 4) were decreased neutrophils, decreased potassium, decreased lymphocyte and decreased haemoglobin.

Table 5 and Table 6 summarise the most common adverse reactions in the NAPOLI-3 study.

Table 5: Adverse reactions with a higher incidence (≥5% difference for all Grades* or ≥2% difference for Grades 3 and 4) with NALIRIFOX versus Gem+NabP treatment in NAPOLI 3

Adverse reaction	NALIRIFOX N=370		Gem+NabP N=379	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal disorders				
Diarrhoea[1]	72	22	37	5
Nausea	59	12	43	2.6
Vomiting[1]	40	7	27	2.1
Constipation	25	0.8	30	2.1
General disorders and administration site conditions				
Fatigue[1]	62	15	63	10
Mucosal inflammation[1]	28	3.8	17	0.8
Peripheral oedema[1]	16	0.3	34	2.4
Pyrexia[1]	11	0.8	24	1.6
Investigations				
Weight decreased	22	3	9	0.3
Metabolism and nutrition disorders				
Decreased appetite	37	9	28	2.6
Dehydration	11	3.2	9	1.1
Skin and subcutaneous tissue disorders				
Alopecia	14	0	31	0.5
Rash[1]	11	0.3	22	1.6
Nail disorder	0.3	0	7	0.3
Vascular disorders				
Haemorrhage[1]	11	2.4	18	3.4
Embolism[1]	11	7	11	5
Respiratory, thoracic and mediastinal disorders				
Dyspnoea[1]	8	0.5	13	2.1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[1]	18	1.6	27	1.1
Infections and infestations				
Pneumonia	2.4	1.6	6	4
Sepsis[1]	1.6	1.1	6	3.4

*NCI CTCAE v5.0
NALIRIFOX=ONIVYDE+oxaliplatin/5-fluorouracil/leucovorin; Gem+NabP=gemcitabine+nab-paclitaxel
[1] Includes multiple related MedDRA Preferred Terms

Table 6: Laboratory abnormalities with an incidence at least 5% higher amongst patients who received NALIRIFOX* than amongst those who received Gem+NabP in NAPOLI 3 **

Laboratory abnormality	NALIRIFOX N=370		Gem-NabP N=379	
	All Grades (%)	Grade 3- or 4 (%)	All Grades (%)	Grade 3 or4 (%)
Haematology				
Haemoglobin decreased	91	10	96	15
Lymphocytes decreased	64	11	76	19
Leukocytes decreased	62	8	77	28
Neutrophils decreased	56	26	65	37
Platelets decreased	55	1.7	75	7
Hepatic				
Alkaline phosphatase increased	45	2.9	35	2.7
Alanine aminotransferase increased	40	2.6	56	4.6

Laboratory abnormality	NALIRIFOX N=370		Gem-NabP N=379	
	All Grades (%)	Grade 3- or 4 (%)	All Grades (%)	Grade 3 or4 (%)
Aspartate aminotransferase increased	38	2.0	49	2.4
Metabolic				
Potassium decreased	62	22	29	8
Sodium increased	11	0	5	0.3
Potassium increased	8	0.6	21	3.0
*NALIRIFOX=ONIVYDE+oxaliplatin/5-fluorouracil/leucovorin; Gem+NabP=gemcitabine+nab-paclitaxel ** Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: NALIRIFOX (range: 294 to 351 patients) and Gem+NabP (range: 303 to 373 patients).				

Description of selected adverse reactions

Description and management advice for key adverse reactions is contained in *section 4.2 – Dose and method of administration* and *section 4.4 – Special warnings and precautions for use.*

Other clinically relevant adverse reactions that were described in clinical studies include:

Cholinergic reactions: ONIVYDE can cause cholinergic reactions manifesting as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis, and intestinal hyperperistalsis with abdominal cramping and early onset diarrhoea. In NAPOLI-1, Grade 1 or 2 cholinergic symptoms other than early diarrhoea occurred in 12 (4.5%) ONIVYDE-treated patients. Six of these 12 patients received atropine and in 1 of the 6 patients, atropine was administered for cholinergic symptoms other than diarrhoea.

Infusion reactions: Infusion reactions, consisting of rash, urticaria, periorbital oedema, or pruritus, occurring on the day of ONIVYDE administration were reported in 3% of patients receiving ONIVYDE or ONIVYDE/FU/LV in NAPOLI-1.

Safety in specific populations

Exploratory exposure-response analyses suggest toxicity is proportional to exposure (see *section 5.2 Pharmacodynamic properties – Pharmacodynamic effects*). Populations with higher exposure may be at higher risk of toxicities.

Patients with hepatic impairment

Elevated bilirubin level is associated with lower SN-38 clearance (see *section 5.1 Pharmacokinetic properties - Pharmacokinetics in specific populations*). In clinical studies of non-liposomal irinotecan administered on a weekly dosage schedule, patients with modestly elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) had a significantly greater likelihood of experiencing first cycle Grade 3 or Grade 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL. See also *section 4.4 – Special warnings and precautions for use - Use in hepatic impairment.*

Female patients

Exposure is higher in female patients than males (see *section 5.1 Pharmacokinetic properties - Pharmacokinetics in specific populations*). In NAPOLI-3, 19% of males (36 out of 189) and 32% of females (55 out of 171) who received ONIVYDE had neutropenia adverse events of Grade ≥3. In NAPOLI-1, 30% of males (20 out of 66) and 24% of females (12 out of 50) who received ONIVYDE had neutropenia adverse events of Grade ≥3.

Asian population

Population pharmacokinetic analysis showed decreased irinotecan and increased SN-38 exposure in the Asian population (see *section 5.1 Pharmacokinetic properties - Pharmacokinetics in specific populations*).

In NAPOLI-1, 33 of the patients who received ONIVYDE in combination with 5-FU/LV were Asian (28%), and 52 of the patients who received ONIVYDE as monotherapy (not an approved usage) were Asian (35%). Grade 3 or 4 diarrhoea occurred in 3% and 15% of these patients, respectively, as well as in 17% and 24% of the complementary (non-Asian) subgroups. Laboratory results for the same groups showed Grade 3 or 4 neutropenia in 52% and 33% of patients who were Asian, and 7% and 7% of those who were not. Neutropenic sepsis occurred in 6% and 10% of patients who were Asian, and 2.4% and 2.1% of those who were not.

In NAPOLI 3, 20 of the patients who received ONIVYDE were Asian (5%). Amongst Asian patients and non-Asian patients, the respective rates of Grade 3 or 4 diarrhoea were 5% and 21%; rates of laboratory results showing Grade 3 or 4 neutropenia were 15% and 25%; and rates of neutropenic sepsis were 5% and 2.3%.

Patients with homozygous UGT1A1 activity

Individuals who are homozygous for the UGT1A1*28 allele (also known as having a UGT1A1 7/7 or *28/*28 genotype) have an increased risk of toxicities, notably neutropenia, with non-liposomal irinotecan hydrochloride treatment. In NAPOLI-1, patients homozygous for the UGT1A1*28 allele (n=7) initiated ONIVYDE at a reduced dose of 50 mg/m^2 in combination with 5-FU/LV. Grade 3 or 4 neutropenia occurred in 2 (29%) of these patients and in 30 (27%) patients not homozygous for the UGT1A1*28 allele who initiated ONIVYDE (in combination with 5-FU/LV) at a dose of 70 mg/m^2. In NAPOLI 3, patients homozygous for the UGT1A1*28 allele (n=39) initiated ONIVYDE at the same starting dose (50 mg/m^2) as patients not homozygous for the UGT1A1*28 allele. Rates of serious or severe (Grade ≥3) treatment-emergent adverse events and of dose reduction were similar regardless of presence of the UGT1A1*28/*28 genotype.

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

In NAPOLI-1, 5 of 8 underweight patients experienced Grade ≥3 adverse reaction, mostly myelosuppression, while 7 of the 8 patients required dose modification such as dose delay, dose reduction or dose discontinuation.

In NAPOLI-3, rates of Grade ≥3 adverse events occurred in 13 (87%) of 15 patients who were underweight and 309 (87%) of 355 patients who were not. ONIVYDE dose reduction was required in 10 (67%) underweight patients and 185 (52%) of those who were not. Adverse events that led to death occurred in 3 (20%) underweight patients and 19 (5%) of those who were not. Discontinuation due to adverse events occurred in 2 (13%) underweight patients and 117 (33%) of those who were not.

Prior Whipple procedure

Amongst patients receiving ONIVYDE+5-FU/LV in NAPOLI-1, serious infections occurred in 9 (30%) of 29 patients with a prior Whipple procedure and 11 (13%) of 88 patients without a prior Whipple procedure. Amongst patients receiving NALIRIFOX in NAPOLI-3, serious infections occurred in 3 (20%) of 15 patients with a prior Whipple procedure and 50 (14%) of 370 patients without a prior Whipple procedure.

Elderly patients

In NAPOLI-1, 41% of patients who received ONIVYDE were at least 65 years of age and 12 patients (10%) were over 75 years of age. The overall toxicity profile of treatment with ONIVYDE+5-FU/LV was broadly similar between age groups. Rates of discontinuation due to adverse events amongst patients <65 years and ≥65 years of age were 8% and 15%, respectively, but Grade 3 or higher and serious treatment emergent adverse reactions were more frequent in patients <65 years (84% and 51%) compared to patients ≥65 years (69% and 44%). Conversely, patients >75 years (n=12) experienced more frequent serious adverse reactions, dose delay, dose reduction and discontinuation compared to patients ≤75 years (n=105).

In NAPOLI-3, 50% of patients who received NALIRIFOX were at least 65 years of age and 7% were 75 years or older. The overall toxicity profile for NALIRIFOX was broadly similar between age groups of <65 years, 65-75 years, and ≥75 years. Rates of discontinuation due to adverse events amongst these groups were 30%, 34% and 36%, respectively.

Postmarketing experience

The following adverse reactions have been identified during post-approval use of ONIVYDE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: hypersensitivity (including anaphylactic reaction and angioedema).

Respiratory, thoracic and mediastinal disorders: interstitial lung disease (including pneumonitis).

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre telephone: 13 11 26 (Australia).

In clinical trials, ONIVYDE was administered at doses up to 210 mg/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.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The active ingredient in ONIVYDE is irinotecan: a water-soluble topoisomerase 1 inhibitor. Topoisomerase 1 relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind reversibly to the topoisomerase I-DNA complex and prevent re-ligation of these single-strand breaks, leading to exposure time-dependent double-strand DNA damage and cell death. SN-38 is lipophilic and inhibits topoisomerase 1 approximately 1000-fold more potently than irinotecan.

Liposomal irinotecan (sucrosofate) has different pharmacokinetic properties to non-liposomal irinotecan hydrochloride (see *section 5.2 Pharmacokinetic properties*). Intravenous administration of both formulations to mice bearing human tumour xenografts resulted in similar systemic and tumour SN-38 exposures when liposomal irinotecan was given at a 5-fold lower dose than non-liposomal irinotecan hydrochloride.

Clinical trials

NAPOLI-3: ONIVYDE in combination with oxaliplatin, 5-FU and LV for the first-line treatment of metastatic pancreatic adenocarcinoma

The safety and efficacy of ONIVYDE in combination with oxaliplatin, 5-fluorouracil and leucovorin (NALIRIFOX) was evaluated in NAPOLI-3, a randomised, multicentre, open-label, active-controlled study that included 770 patients with metastatic pancreatic adenocarcinoma who had not previously received chemotherapy in the metastatic setting. Randomisation was stratified by region, liver metastases and ECOG performance status. Patients were randomised (1:1) to the following treatment arms:

- NALIRIFOX: ONIVYDE 50 mg/m^2 as an intravenous infusion over 90 minutes, followed by oxaliplatin 60 mg/m^2 as an intravenous infusion over 120 minutes, followed by leucovorin 400 mg/m^2 intravenously over 30 minutes, followed by 5-FU 2,400 mg/m^2 intravenously over 46 hours, administered every 2 weeks.
- Gem+NabP: Nab-paclitaxel 125 mg/m^2 as an intravenous infusion over 35 minutes, followed by gemcitabine 1,000 mg/m^2 intravenously over 30 minutes on days 1, 8 and 15 of each 28-day cycle.

Patients homozygous for the UGT1A1*28 allele initiated ONIVYDE at the same dose (50 mg/m^2 ONIVYDE) and were closely monitored for safety. Tumour status assessments were conducted according to RECIST v1.1 at baseline and every 8 weeks thereafter. Treatment continued until RECIST-defined disease progression or unacceptable toxicity.

The primary efficacy endpoint was overall survival (OS). Investigator-assessed progression-free survival (PFS) and objective response rate (ORR) were secondary efficacy endpoints.

Baseline demographics and patient characteristics were: median age of 65 years (range: 20-85); 50% age 65 or older; 56% male; 83% Caucasian; 5% Asian; 3% Black or African American; ECOG performance status was 0 or 1 in 43% and 57% of patients; 80% had liver metastases.

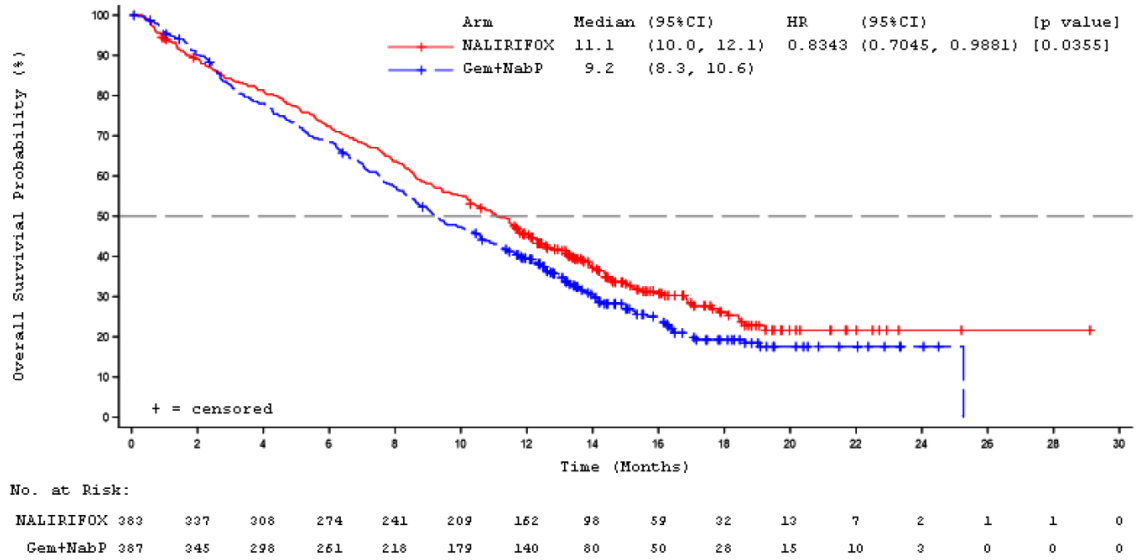
The efficacy results of NAPOLI-3 are summarised in Table 7, Figure 1 and Figure 2.

Table 7: Efficacy results from the NAPOLI-3 study

	NALIRIFOX (N=383)	**Gem+NabP** (N=387)
Overall survival (OS)		
Number of deaths, n (%)	259 (68)	285 (74)
Median OS (months)	11.1	9.2
(95% CI)	(10.0, 12.1)	(8.3, 10.6)
Hazard ratio (95% CI)*	0.83 (0.70, 0.99)	
p-value†	0.04	
Progression-free survival (PFS)		
Death or progression events, n (%)	249 (65)	259 (67)
Median PFS (months)	7.4	5.6
(95% CI)	(6.0, 7.7)	(5.3, 5.8)
Hazard ratio (95% CI)*	0.69 (0.58, 0.83)	
p-value†	< 0.0001	
Objective response rate (ORR)#		
ORR (95% CI)	41.8 (36.8, 46.9)	36.2 (31.4, 41.2)
CR, n (%)	1 (0.3)	1 (0.3)
PR, n (%)	159 (41.5)	139 (35.9)

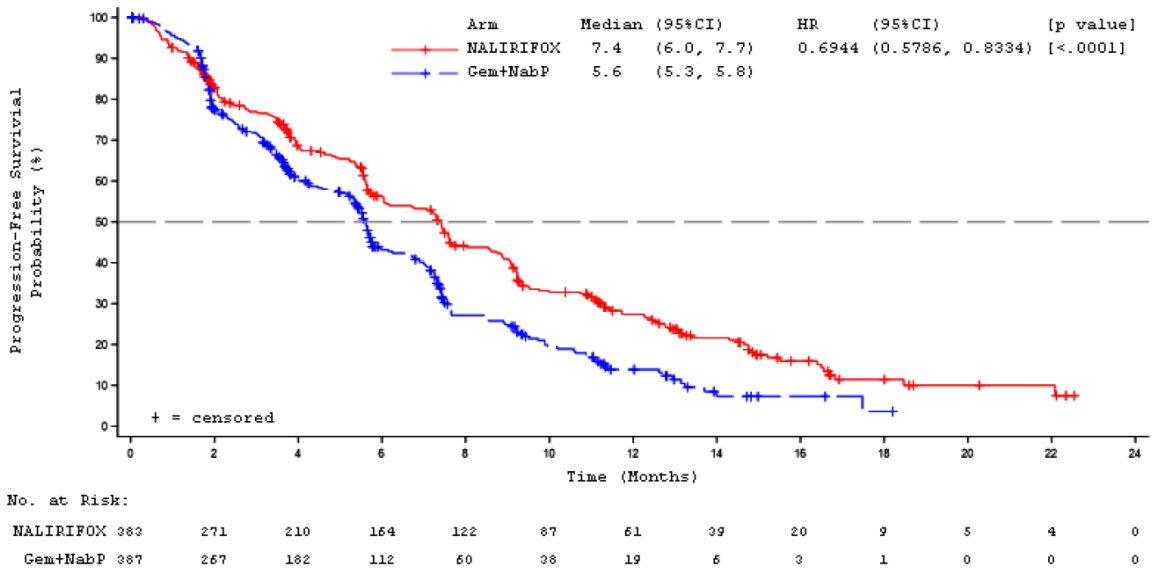
NALIRIFOX= ONIVYDE +oxaliplatin/5-fluorouracil/leucovorin; Gem+NabP=gemcitabine+nab-paclitaxel; CI=confidence interval
* Based on the stratified Cox proportional hazard model
† Based on stratified log-rank test
# A significant difference in response rates was not demonstrated
Abbreviations: CR=complete response, PR=partial response; CI=confidence interval, CMH= Cochran–Mantel–Haenszel

Figure 1: Kaplan-Meier curve for overall survival (NAPOLI-3 ITT population)



CI=confidence interval, HR=hazard ratio

Figure 2: Kaplan-Meier curve for progression-free survival (NAPOLI-3 ITT population)



CI=confidence interval, HR=hazard ratio

NAPOLI-1: ONIVYDE in combination with 5-FU and LV for the treatment of metastatic pancreatic adenocarcinoma after gemcitabine-based therapy

The efficacy of ONIVYDE was evaluated in the NAPOLI-1 study, 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 ≥30g/L. Patients were randomised (1:1:1) to the following treatment arms:

- ONIVYDE plus 5-FU/ LV (n=117): ONIVYDE 70 mg/m^2 (based on irinotecan free base; equivalent to 80 mg/m^2 of irinotecan hydrochloride trihydrate) as an intravenous infusion over 90 minutes, followed by LV 400 mg/m^2 intravenously over 30 minutes, followed by 5-FU 2,400 mg/m^2 intravenously over 46 hours, every 2 weeks.
- ONIVYDE monotherapy (n=151): 100 mg/m^2 as an intravenous infusion over 90 minutes every 3 weeks.
- 5-FU/LV (n=149): received LV 200 mg/m^2 intravenously over 30 minutes, followed by 5-FU 2,000 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 treatment at a reduced dose (50 mg/m^2 ONIVYDE plus 5-FU/LV or 70 mg/m^2 ONIVYDE monotherapy), see *section 4.2 -Dose and method of administration*. Treatment continued until disease progression or unacceptable toxicity.

Patients enrolled in the NAPOLI-1 study 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 39.6 g/L, 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+5FU/LV arm.

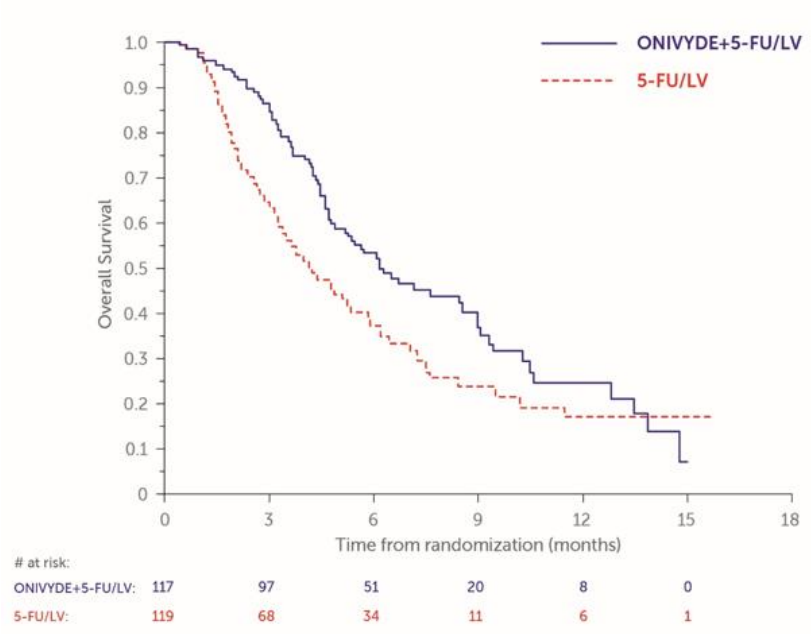
The primary efficacy measure was overall survival (OS). Additional outcome measures included progression-free survival (PFS) and objective response rate (ORR). Assessments were conducted at baseline and every 6 weeks thereafter. Comparison of the ONIVYDE+5FU/LV arm to the 5-FU/LV arm demonstrated improvement in overall survival and the other efficacy outcomes summarised in Table 8 and Figure 3. Comparison of the ONIVYDE monotherapy arm to the 5-FU/LV control arm did not demonstrate evidence of an improvement in overall survival compared to the 5-FU/LV control arm (hazard ratio=0.99, log-rank two-sided p-value=0.9416).

Table 8: Efficacy results from the NAPOLI-1 study

	ONIVYDE+5-FU/LV (N=117)	**5-FU/LV (N=119)**
Overall survival (OS)		
Number of deaths, n (%)	75 (64)	80 (67)
Median overall survival (months) [1]	6.1	4.2
(95% CI)	(4.8, 8.9)	(3.3, 5.3)
Hazard ratio (95% CI)[2]	0.67 (0.49 – 0.92)	
p-value[3]	0.0122	
Progression-free survival (PFS) [4]		
Death or progression events, n (%)	83 (71)	92 (77)
Median progression-free survival (months) [1]	3.1	1.5
(95% CI)	(2.7, 4.2)	(1.4, 1.8)
Hazard ratio (95% CI) [2]	0.56 (0.41 – 0.75)	
Objective response rate (ORR) [4]		
Patients with a response, n	19	1
ORR (%)	16.2	0.8
95% CI of rate [5]	9.6, 22.9	0.0, 2.5

1. Kaplan-Meier estimate
2. Cox model analysis
3. Unstratified log-rank test
4. Responses defined per RECIST guidelines v1.1; comparison between arms not formally tested for statistical significance due to statistical design
5. Based on Normal approximation

Figure 3: Kaplan-Meier curve for overall survival - (NAPOLI-1 ITT population)



Prospective subgroup analyses based on stratification factors did not identify a differential treatment effect on OS.

Pharmacodynamic effects

NAPOLI-3: ONIVYDE in combination with oxaliplatin, 5-FU and LV For the first-line treatment of metastatic pancreatic adenocarcinoma

An exploratory exposure-safety analysis of NAPOLI-3 data suggested that the risk of Grade ≥3 diarrhoea or neutropenia increases with increasing exposures of both irinotecan and SN-38.

NAPOLI-1: ONIVYDE in combination with 5-FU and LV for the treatment of metastatic pancreatic adenocarcinoma after gemcitabine-based therapy

An exploratory exposure-safety analysis of pooled data from 353 patients who received ONIVYDE either as monotherapy or in combination with 5-FU/LV in NAPOLI-1, suggested that 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. Exploratory exposure-efficacy analyses suggested a positive correlation.

5.2 PHARMACOKINETIC PROPERTIES

ONIVYDE (liposome-encapsulated irinotecan as sucrosofate) has different pharmacokinetics to non-liposomal irinotecan hydrochloride.

Absorption

The plasma pharmacokinetics of total (liposomal and non-liposomal) irinotecan and total SN-38were evaluated in patients with cancer who received ONIVYDE (as monotherapy or as part of combination therapy) at doses between 35 mg/m^2 and 155 mg/m^2. The pharmacokinetic parameters of total irinotecan and total SN-38, following the administration of ONIVYDE at 70 mg/m^2 as a single agent or as part of combination chemotherapy, and at 50mg/m^2 in the NALIRIFOX regimen, are presented in Table 9.

Table 9: Summary of total irinotecan and total SN-38 pharmacokinetics after ONIVYDE administration

Dose (mg/m^2)	Descriptive statistic	Total irinotecan			Total SN-38	
		C_{max} [µg/mL]	AUC_{SS} [day·µg/mL]	$t_{1/2}$ [day]	C_{max} [ng/mL]	AUC_{SS} [day·ng/mL]
50 (n=360)	Geometric mean	25.1	37.8	1.93	2.09	12.1
	Geometric CV (%)	19	74	14	42	47
70 (n=246)	Geometric mean	30.8	50.4	1.87	2.64	14.7
	Geometric CV (%)	20	75	26	65	58
AUC_{SS} = area under the plasma concentration curve at steady-state; C_{max} = maximum plasma concentration; CV = coefficient of variation; n = number of patients contributing data at this dose; $t_{1/2}$ = terminal elimination half-life						

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.

Distribution

Direct measurement of liposomal irinotecan shows that 95% of irinotecan remains liposome-encapsulated during circulation, and the ratios between total and encapsulated forms did not change with time from 0 to 170 hours post-dose. The mean volume of distribution of ONIVYDE is 4 L (obtained from population pharmacokinetic analysis).

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

The metabolism of liposomal irinotecan has not been evaluated. Irinotecan is subject to extensive metabolic conversion by various enzyme systems, including carboxylesterases 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 hydrolysed by carboxylesterase to release SN-38. In the population PK analysis of liposomal irinotecan, UGT1A1*28 7/7 homozygous status (10.6%) had no effect on SN-38 clearance compared with patients not homozygous for UGT1A1*28 7/7.

Excretion

The disposition of ONIVYDE has not been elucidated in humans. Following administration of non-liposomal irinotecan hydrochloride, 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 hydrochloride in two patients ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/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 non-liposomal irinotecan. Faecal excretion was the major route of excretion in rats, accounting for approximately 80% of the total radioactivity dose of liposomal encapsulated 14C-irinotecan over 168 hours.

Pharmacokinetics in specific populations

Age, sex, ethnicity, renal and hepatic impairment

The population pharmacokinetic analyses suggest that age (20 to 87 years) and BSA (1.15 to 2.88 m^2) had no clinically meaningful effect on the exposure of irinotecan and SN-38 after administration of ONIVYDE.

Irinotecan and SN-38 AUC in female patients were 28% and 32% higher, respectively, than those in male patients. Irinotecan AUC in patients of Asian ethnicity was 32% lower than that in non-Asian patients, but SN-38 C_{max} was 7% higher in Asian than non-Asian patients. The exposures of irinotecan and SN-38 in patients with mild or moderate renal impairment were comparable to patients with normal renal function after adjusting for BSA. The exposures of irinotecan and SN-38 in patients with mild hepatic impairment (based on NCI score) were comparable to patients with normal hepatic function. There was insufficient data in patients with severe renal impairment (CLcr <30 mL/min) or in patients with moderate and severe hepatic impairment to assess their effects on the exposures of irinotecan and SN-38. Increased AST/ALT had no effect on irinotecan clearance; however, increased bilirubin level was associated with lower SN-38

clearance. SN-38 AUC was increased by 32% in patients with bilirubin level of 1.14 mg/dL (95th of the overall population) compared with that of median bilirubin level of 0.44 mg/dL. No data are available in patients with bilirubin >2.8 mg/dL.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No studies to assess the genotoxic potential have been performed with ONIVYDE. Irinotecan and SN-38 were genotoxic *in vitro* in the chromosomal aberration test in Chinese hamster ovary cells, and irinotecan in the *in vivo* micronucleus test in mice. Irinotecan or SN-38 was not mutagenic in the Ames assay.

Carcinogenicity

Carcinogenicity studies with ONIVYDE were not conducted. For irinotecan, in rats treated once a week for 13 weeks at 12 or 150 mg/m² followed by a 91-week recovery period, there was a significant linear trend with dose for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The concentrated injection contains hepes (buffer), sodium chloride (isotonicity reagent), distearoylphosphatidylcholine, cholesterol, sodium methoxy PEG-40-carbonyl-distearoylphosphatidylethanolamine, sucrosofate (drug entrapment agent) and water for injections.

Note for patients on a controlled sodium diet: each mL of ONIVYDE contains 0.144 mmol sodium, which is 3.31 mg sodium.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2 °C to 8 °C).

Do not freeze.

Protect from light.

Contains no antimicrobial preservative.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type

ONIVYDE concentrated solution for injection is packed in a 10 mL vial (type I glass) with a 20 mm, grey chlorobutyl stopper and a 20 mm aluminium seal with a flip-off cap, containing irinotecan sucrosofate equivalent to 43 mg irinotecan or 50 mg irinotecan hydrochloride trihydrate, encapsulated in liposomes, as a dispersion.

ONIVYDE is for single use in one patient only.

Pack size

1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

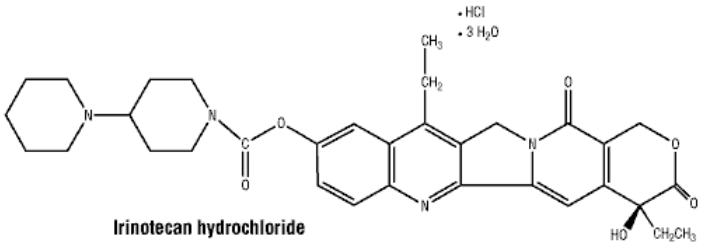
ONIVYDE is a cytotoxic medicine and caution should be exercised in handling it. The use of gloves, goggles and protective clothing when handling or administering ONIVYDE is recommended. If the solution contacts the skin, the skin should be washed immediately and thoroughly with soap and water. If the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

6.7 PHYSICOCHEMICAL PROPERTIES

The active component of ONIVYDE is irinotecan hydrochloride which has the chemical name (4S)-4, 11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino) carbonyloxy]-1*H*-pyrano[3', 4':6, 7]indolizino[1, 2-*b*]quinoline-3, 14(4*H*, 12*H*) dione hydrochloride trihydrate. Irinotecan hydrochloride has the molecular formula: $C_{33}H_{38}N_4O_6.HCl.3H_2O$ (MW= 677.19).

Irinotecan hydrochloride is a semisynthetic derivative of camptothecin, an alkaloid extracted from plants such as *Camptotheca acuminata*. It is a pale yellow to yellow crystalline powder and is slightly soluble in water and organic solvents.

Chemical Structure



Irinotecan hydrochloride

CAS number:

136572-09-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4).

8 SPONSOR

Servier Laboratories (Aust.) Pty. Ltd.
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9 DATE OF FIRST APPROVAL

19 December 2016

10 DATE OF REVISION

06 March 2024

Summary table of changes

Section(s) Changed	Summary of new information
4.2, 4.4, 4.8, 5.1	New indication – 1st line use