SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ONIVYDE pegylated liposomal 4.3 mg/ml concentrate for dispersion for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One 10 ml vial of concentrate contains 43 mg irinotecan anhydrous free base (as irinotecan sucrosofate salt in a pegylated liposomal formulation).

One ml of concentrate contains 4.3 mg irinotecan anhydrous free base (as irinotecan sucrosofate salt in a pegylated liposomal formulation).

Excipient with known effect

One ml of concentrate contains 0.144 mmol (3.31 mg) sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for dispersion for infusion.

White to slightly yellow opaque isotonic liposomal dispersion.

The concentrate has a pH of 7.2 and an osmolality of 295 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ONIVYDE pegylated liposomal is indicated in:
- in combination with oxaliplatin, 5-fluorouracil (5-FU) and leucovorin (LV) for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas,
-in combination with 5-FU and LV for the treatment of metastatic adenocarcinoma of the pancreas in adult patients who have progressed following gemcitabine based therapy.

4.2 Posology and method of administration

ONIVYDE pegylated liposomal must only be prescribed and administered to patients by healthcare professionals experienced in the use of anticancer therapies.

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

Posology

ONIVYDE pegylated liposomal should not be administered as a single agent and should be continued until disease progression or no longer tolerated by the patient.

ONIVYDE pegylated liposomal in combination with oxaliplatin, 5-fluorouracil and leucovorin:
ONIVYDE pegylated liposomal, oxaliplatin, LV and 5-FU should be administered sequentially. The recommended dose of ONIVYDE pegylated liposomal is 50 mg/m² intravenously over 90 minutes, followed by oxaliplatin 60 mg/m^2 intravenously over 120 minutes, followed by LV 400 mg/m2 intravenously over 30 minutes, followed by 5-FU 2,400 mg/m^2 intravenously over 46 hours. This regimen should be administered every 2 weeks.
Oxaliplatin may be discontinued if not well tolerated and treatment with ONIVYDE pegylated liposomal + 5-FU/LV can continue.

The recommended starting dose of ONIVYDE pegylated liposomal in patients known to be homozygous for UGT1A1*28 allele is unchanged and remains 50 mg/m2 administered intravenously over 90 minutes (see sections 5.1 and 5.2).

ONIVYDE pegylated liposomal in combination with 5-fluorouracil and leucovorin:
ONIVYDE pegylated liposomal, leucovorin and 5-fluorouracil should be administered sequentially. The recommended dose and regimen of ONIVYDE pegylated liposomal 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.

A reduced starting dose of ONIVYDE pegylated liposomal of 50 mg/m^2 should be considered for patients known to be homozygous for the UGT1A1*28 allele (see sections 4.8 and 5.1). A dose increase of ONIVYDE pegylated liposomal to 70 mg/m^2 should be considered if tolerated in subsequent cycles.

Pre-medication
It is recommended that patients receive pre-medication with standard doses of dexamethasone (or an equivalent corticosteroid) together with a $5HT_3$ antagonist (or other antiemetic) at least 30 minutes prior to ONIVYDE pegylated liposomal infusion.

Dose adjustments
All dose modifications should be based on the worst preceding toxicity. The LV dose does not require adjustment.

ONIVYDE pegylated liposomal in combination with oxaliplatin, 5-fluorouracil and leucovorin:

Table 1 Recommended dose modifications for ONIVYDE pegylated liposomal + oxaliplatin/5-FU/LV

Toxicity grade (value) by NCI CTCAE†	***ONIVYDE pegylated liposomal/Oxaliplatin/5-FU adjustments***	
Haematological toxicities		
Neutropenia	A new cycle of therapy should not begin until the absolute neutrophil count is ≥2,000/mm^3 (2x10^9/L)	
Grade 3 or Grade 4 (<1,000 cells/mm^3) or Neutropenic fever	***First occurrence***	Reduce ONIVYDE pegylated liposomal dose to 80% of initial dose Reduce oxaliplatin and 5-FU dose by 20%
	Second occurrence	Reduce ONIVYDE pegylated liposomal dose to 65% of initial dose Reduce oxaliplatin and 5-FU dose by an additional 15%
	Third occurrence	Reduce ONIVYDE pegylated liposomal dose to 50% of initial dose Reduce oxaliplatin and 5-FU dose by an additional 15%
	Fourth occurence	Discontinue treatment
Thrombocytopenia Leukopenia	A new cycle of therapy should not begin until the platelet count is ≥100,000/mm^3 (100x10^9/L). Dose modifications for leukopenia and thrombocytopenia are based on NCI CTCAE toxicity grading and are the same as recommended for neutropenia above.	
Non-haematological toxicities‡		
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 2	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	***First occurrence***	Reduce ONIVYDE pegylated liposomal dose to 80% of initial dose Reduce oxaliplatin and 5-FU dose by 20%
	Second occurrence	Reduce ONIVYDE pegylated liposomal dose to 65% of initial dose Reduce oxaliplatin and 5-FU dose by an additional 15%
	Third occurrence	Reduce ONIVYDE pegylated liposomal dose to 50% of initial dose Reduce oxaliplatin and 5-FU dose by an additional15%
	Fourth occurrence	Discontinue treatment
All other toxicities* *Grade 3 or 4*	***First occurrence***	Reduce ONIVYDE pegylated liposomal dose to 80% of initial dose Reduce oxaliplatin and 5-FU dose by 20%
	Second	Reduce ONIVYDE pegylated liposomal dose to65%

Toxicity grade (value) by NCI CTCAE†	***ONIVYDE pegylated liposomal/Oxaliplatin/5-FU adjustments***	
	occurrence	of initial dose Reduce oxaliplatin and 5-FU dose by an additional 15%
	Third occurrence	Reduce ONIVYDE pegylated liposomal dose to 50% of initial dose Reduce oxaliplatin and 5-FU dose by an additional 15%
	Fourth occurrence	Discontinue treatment
For Grade ≥ 3 nausea and vomiting	Reduce dose only if occurs despite optimal anti-emetic therapy	
Hand foot syndrome: Grade 3 or 4	***First occurrence***	Discontinue treatment
Any grade neurocerebellar or ≥ Grade 2 cardiac toxicity	***First occurrence***	Discontinue treatment
Anaphylactic reaction	***First occurrence***	Discontinue treatment
Interstitial lung disease	***First occurrence***	Discontinue treatment

* Excludes asthenia and anorexia;
† NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, current version

Patients homozygous for the UGT1A1*28 allele should initiate ONIVYDE pegylated liposomal at the same dose and the same dose reduction requirements should apply.

ONIVYDE pegylated liposomal in combination with 5-fluorouracil and leucovorin:
For patients who start treatment with 50 mg/m^2 ONIVYDE pegylated liposomal and do not dose escalate to 70 mg/m^2, the recommended first dose reduction is to 43 mg/m^2 and the second dose reduction is to 35 mg/m^2. Patients who require further dose reduction should discontinue treatment.

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

Table 2~~1~~: Recommended dose modifications for ONIVYDE pegylated liposomal +5-FU/LV for Grade 3-4 toxicities for patients not homozygous for UGT1A1*28

Toxicity grade (value) by NCI CTCAE ~~v 4.0~~[1]	**ONIVYDE pegylated liposomal /5-FU adjustment (for patients not homozygous for UGT1A1*28)**	
Haematological toxicities		
Neutropenia	A new cycle of therapy should not begin until the absolute neutrophil count is ≥ 1,500 cells/mm^3	
***Grade 3 or Grade 4 (< 1,000 cells/mm^3)* or**	***First occurrence***	Reduce ONIVYDE pegylated liposomal dose to 50 mg/m^2 Reduce 5-FU dose by 25% (1,800 mg/m^2).

Toxicity grade (value) by NCI CTCAE ~~v 4.0~~[1]	**ONIVYDE pegylated liposomal /5-FU adjustment (for patients not homozygous for UGT1A1*28)**	
Neutropenic fever	***Second occurrence***	Reduce ONIVYDE pegylated liposomal dose to 43 mg/m^2 Reduce 5-FU dose by an additional 25% (1,350 mg/m^2).
	Third occurrence	Discontinue treatment
Thrombocytopenia **Leukopenia**	A new cycle of therapy should not begin until the platelet count is ≥ 100,000 platelets/mm^3 Dose modifications for leukopenia and thrombocytopenia are based on NCI CTCAE toxicity grading and are the same as recommended for neutropenia above.	
Non-haematological 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 2	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	***First occurrence***	Reduce ONIVYDE pegylated liposomal dose to 50 mg/m^2 Reduce 5-FU dose by 25% (1,800 mg/m^2)
	Second occurrence	Reduce ONIVYDE pegylated liposomal dose to 43 mg/m^2 Reduce 5-FU dose by an additional 25% (1,350 mg/m^2)
	Third occurrence	Discontinue treatment
Nausea/vomiting	A new cycle of therapy should not begin until nausea/vomiting resolves to ≤ Grade 1 or baseline	
Grade 3 or 4 *(despite antiemetic therapy)*	***First occurrence***	Optimise antiemetic therapy Reduce ONIVYDE pegylated liposomal dose to 50 mg/m^2
	Second occurrence	Optimise antiemetic therapy Reduce ONIVYDE pegylated liposomal dose to 43 mg/m^2
	Third occurrence	Discontinue treatment
Hepatic, renal, respiratory or other[2] **toxicities** ***Grade 3 or 4***	A new cycle of therapy should not begin until the adverse reaction resolves to ≤ Grade 1	
	First occurrence	Reduce ONIVYDE pegylated liposomal dose to 50 mg/m^2 Reduce 5-FU dose by 25% (1,800 mg/m^2)
	Second occurrence	Reduce ONIVYDE pegylated liposomal dose to 43 mg/m^2 Reduce 5-FU dose by an additional 25% (1,350 mg/m^2)
	Third occurrence	Discontinue treatment
Anaphylactic reaction	***First occurrence***	Discontinue treatment

Toxicity grade (value) by NCI CTCAE ~~v 4.0~~[1]	**ONIVYDE pegylated liposomal /5-FU adjustment (for patients not homozygous for UGT1A1*28)**	
Interstitial Lung Disease	***First occurrence***	Discontinue treatment

[1] NCI CTCAE ~~v 4.0~~ = National Cancer Institute Common Terminology Criteria for Adverse Events, current version ~~4.0~~

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

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

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

[1] NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, current version

[2] Excludes asthenia and anorexia; asthenia and Grade 3 anorexia do not require dose adjustment.

[3] In case of a dose increase of ONIVYDE pegylated liposomal to 70 mg/m^2 if tolerated in subsequent cycles, recommended dose modifications should follow Table 2.

<u>*Special populations*</u>

Hepatic impairment

No dedicated hepatic impairment study has been conducted with ONIVYDE pegylated liposomal. The use of ONIVYDE pegylated liposomal should be avoided in patients with bilirubin > 2.0 mg/dl, or aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 2.5 times upper limit of normal (ULN) or > 5 times ULN if liver metastasis is present (see section 4.4).

Renal impairment

No dedicated renal impairment study has been conducted with ONIVYDE pegylated liposomal. No dose adjustment is recommended in patients with mild to moderate renal impairment (see sections 4.4 and 5.2). ONIVYDE pegylated liposomal is not recommended for use in patients with severe renal impairment (CLcr < 30 ml/min).

Elderly

Forty-nine percent (49.6 %) in NAPOLI-3 and forty-one percent (41%) in NAPOLI-1 of patients treated with ONIVYDE pegylated liposomal were ≥ 65 years. No dose adjustment is recommended.

Paediatric population

The safety and efficacy of ONIVYDE pegylated liposomal in children and adolescents aged ≤ 18 years have not yet been established. No data are available.

Method of administration
ONIVYDE pegylated liposomal is for intravenous use. The concentrate must be diluted prior to administration and given as a 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 pegylated liposomal is a cytotoxic medicinal product. The use of gloves, goggles and protective clothing when handling or administering ONIVYDE pegylated liposomal is recommended. Pregnant staff should not handle ONIVYDE pegylated liposomal.

4.3 Contraindications

History of severe hypersensitivity to irinotecan or to any of the excipients listed in section 6.1.

Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

General

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

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

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

Myelosuppression/neutropenia

Complete blood cell count monitoring is recommended during ONIVYDE pegylated liposomal treatment. Patients should be aware of the risk of neutropenia and the significance of fever. Febrile neutropenia (body temperature > 38°C and neutrophil count ≤ 1,000 cells/mm³) should be urgently treated in the hospital with broad-spectrum intravenous antibiotics. Sepsis with neutropenic fever and consequent septic shock with fatal outcome has been observed in patients with metastatic pancreatic adenocarcinoma treated with ONIVYDE pegylated liposomal.
In patients who experienced severe haematological events, a dose reduction or treatment discontinuation is recommended (see section 4.2). Patients with severe bone marrow failure should not be treated with ONIVYDE pegylated liposomal.

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

Patients with deficient glucuronidation of bilirubin, such as those with Gilbert's syndrome, may be at greater risk of myelosuppression when receiving therapy with ONIVYDE pegylated liposomal.

Immunosuppressive effects and vaccines

Administration of live or live attenuated vaccines in patients immunocompromised by chemotherapeutic medicinal products including ONIVYDE pegylated liposomal may result in serious or fatal infections; therefore, vaccination with a live vaccine should be avoided. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Interactions with strong CYP3A4 inducers

ONIVYDE pegylated liposomal should not be administered with strong CYP3A4enzyme inducers such as anticonvulsants (phenytoin, phenobarbital or carbamazepine), rifampicin, rifabutin and St. John's wort unless there are no therapeutic alternatives. The appropriate starting dose for patients taking these anticonvulsants or other strong inducers has not been defined. Consideration should be given to substituting with nonenzyme inducing therapies at least 2 weeks prior to initiation of ONIVYDE pegylated liposomal therapy (see section 4.5).

Interactions with strong CYP3A4 inhibitors or strong UGT1A1 inhibitors
ONIVYDE pegylated liposomal should not be administered with strong CYP3A4enzyme inhibitors (e.g. grapefruit juice, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole). Strong CYP3A4 inhibitors should be discontinued at least 1 week prior to starting ONIVYDE pegylated liposomal therapy. ONIVYDE pegylated liposomal should not be administered with strong UGT1A inhibitors (e.g. atazanavir, gemfibrozil, indinavir) unless there are no therapeutic alternatives.

Diarrhoea

ONIVYDE pegylated liposomal can cause severe and life-threatening diarrhoea. ONIVYDE pegylated liposomal must not be administered to patients with bowel obstruction, and chronic inflammatory bowel disease.
Diarrhoea can occur early (onset in ≤ 24 hours after starting ONIVYDE pegylated liposomal) or late (> 24 hours) (see section 4.8).
In patients experiencing early diarrhoea or cholinergic symptoms, prophylactic or, therapeutic atropine should be considered unless contraindicated. Patients should be made aware of the risk of delayed diarrhoea which can be debilitating and, on rare occasions, life threatening since persistent loose or watery stools can result in dehydration, electrolyte imbalance, colitis, gastrointestinal (GI) ulceration, infection or sepsis.
As soon as the first liquid stool occurs, the patient should start drinking large volumes of beverages containing electrolytes. Patients should have loperamide (or equivalent) readily available to begin treatment for late diarrhoea. Loperamide should be initiated at first occurrence of poorly formed or loose stools or at the earliest onset of bowel movements more frequent than normal (maximum of 16 mg/day). Loperamide should be given until the patient

is without diarrhoea for at least 12 hours. To help avoid severe diarrhoea, stop all lactose-containing products, maintain hydration and eat a low-fat diet.

If diarrhoea persists while the patient is on loperamide for more than 24 hours, adding oral antibiotic support (e.g. fluoroquinolone for 7 days) should be considered. Loperamide should not be used for more than 48 consecutive hours due to risk of paralytic ileus. If diarrhoea persists for more than 48 hours, stop loperamide, monitor and replace fluid electrolytes and continue antibiotic support until resolution for accompanying symptoms.
A new cycle of therapy should not begin until diarrhoea resolves to ≤ Grade 1 2-3 stools/day more than pre-treatment frequency).
Following Grade 3 or 4 diarrhoea, the subsequent dose of ONIVYDE pegylated liposomal should be reduced~~,~~ (see section 4.2).

Cholinergic reactions

Early onset diarrhoea may be accompanied by cholinergic symptoms such as rhinitis, increased salivation, flushing, diaphoresis, bradycardia, miosis and hyperperistalsis. In case of cholinergic symptoms atropine should be administered.

Hypersensitivity reaction including acute infusion related reactions

Infusion reactions primarily consisting of rash, urticaria, periorbital oedema or pruritus were reported in patients receiving ONIVYDE pegylated liposomal treatment. New events (all grade 1 or grade 2) occurred generally early during ONIVYDE pegylated liposomal treatment, with only 2 out of 10 patients noted with events after the fifth dose. Hypersensitivity reactions, including acute infusion reaction, anaphylactic/anaphylactoid reaction and angioedema may occur. ONIVYDE pegylated liposomal should be discontinued in case of severe hypersensitivity reactions (see section 4.2).

Prior Whipple procedure

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

Vascular disorders

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

Pulmonary toxicity

Interstitial Lung Disease (ILD)-like events leading to fatalities have occurred in patients receiving non-liposomal irinotecan. In NAPOLI-3 study, pneumonitis was reported in 0.3% of patients receiving ONIVYDE pegylated liposomal in combination with oxaliplatin and 5-FU/LV. Risk factors include pre-existing lung disease, use of pneumotoxic medicinal products, colony stimulating factors or having previously received radiation therapy. Patients with risk factors should be closely monitored for respiratory symptoms before and during ONIVYDE pegylated liposomal therapy. A reticulo-nodular pattern on chest X-ray was observed in a small percentage of patients enrolled in a clinical study with irinotecan. New or progressive dyspnoea, cough, and fever should prompt interruption of ONIVYDE pegylated

liposomal treatment, pending diagnostic evaluation. ONIVYDE pegylated liposomal should be discontinued in patients with a confirmed diagnosis of ILD (see section 4.2).

Hepatic impairment

Patients with hyperbilirubinaemia had higher concentrations for total SN38 (see section 5.2) and therefore the risk of neutropenia is increased. Regular monitoring of complete blood counts should be conducted in patients with total bilirubin of 1.0-2.0 mg/dl. Caution should be exercised in patients with hepatic impairment (bilirubin > 2 times upper limit of normal [ULN]; transaminases > 5 times ULN). Caution is required when ONIVYDE pegylated liposomal is given in combination with other hepatotoxic medicinal products, especially in patients with pre-existing hepatic impairment.

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

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

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Information about drug interactions with ONIVYDE pegylated liposomal is referenced from the published scientific literature for non-liposomal irinotecan.

Interaction affecting the use of ONIVYDE pegylated liposomal

Strong CYP3A4 inducers
Patients receiving concomitant non-liposomal irinotecan and CYP3A4 enzyme-inducing anticonvulsants phenytoin, phenobarbital or carbamazepine have substantially reduced exposure to irinotecan (AUC reduction by 12% with St John's wort, 57%-79% with phenytoin, phenobarbital, or carbamazepine) and SN-38 (AUC reduction by 42% with St John's wort, 36%-92% with phenytoin phenobarbital, or carbamazepine). Therefore, co-administration of ONIVYDE pegylated liposomal with inducers of CYP3A4 may reduce systemic exposure of ONIVYDE pegylated liposomal.

Strong CYP3A4 inhibitors and UGT1A1 inhibitors
Patients receiving concomitant non-liposomal irinotecan and ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased SN-38 exposure by 109%. Therefore, co-administration of ONIVYDE pegylated liposomal with other inhibitors of CYP3A4 (e.g. grapefruit juice, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) may increase systemic exposure of ONIVYDE pegylated liposomal. Based on the drug interaction of non-liposomal irinotecan and

ketoconazole, co-administration of ONIVYDE pegylated liposomal with other inhibitors of UGT1A1 (e.g. atazanavir, gemfibrozil, indinavir, regorafenib) may also increase systemic exposure of ONIVYDE pegylated liposomal.

Co-administration of ONIVYDE pegylated liposomal+5-FU/LV does not alter the pharmacokinetics of ONIVYDE pegylated liposomal based on the population pharmacokinetic analysis.

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.

No interaction of ONIVYDE pegylated liposomal with other medicinal products is known.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females

Women of childbearing potential should use effective contraception during ONIVYDE pegylated liposomal treatment and 7 months thereafter. Males should use condoms during ONIVYDE pegylated liposomal treatment and 4 months thereafter.

Pregnancy

There are no adequate data on the use of ONIVYDE pegylated liposomal in pregnant women. ONIVYDE pegylated liposomal 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 pegylated liposomal should not be used during pregnancy unless clearly necessary. If ONIVYDE pegylated liposomal 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.

Breast-feeding

It is unknown whether ONIVYDE pegylated liposomal or its metabolites are excreted into human milk. Because of the potential for serious adverse reactions of ONIVYDE pegylated liposomal in breast-feeding infants, ONIVYDE pegylated liposomal is contraindicated during breast-feeding (see section 4.3). Patients should not breast-feed until one month after the last dose.

Fertility

There are no data on the impact of ONIVYDE pegylated liposomal on human fertility. Non-liposomal irinotecan was shown to cause atrophy of male and female reproductive organs after multiple daily irinotecan doses in animals (see section 5.3). Prior to starting the administration of ONIVYDE pegylated liposomal consider advising patients on the preservation of gametes.

4.7 Effects on ability to drive and use machines

ONIVYDE pegylated liposomal has moderate influence on the 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

ONIVYDE pegylated liposomal in combination with oxaliplatin, 5-fluorouracil and leucovorin (NALIRIFOX):
The following adverse reactions, related to the administration of ONIVYDE pegylated liposomal, were reported in 370 patients treated in combination with oxaliplatin/5-FU/LV, who had not previously received chemotherapy for metastatic adenocarcinoma of the pancreas.
The most common adverse reactions (incidence ≥20%) were diarrhoea, nausea, vomiting, decreased appetite, fatigue, asthenia, neutropenia, neutrophil count decreased and anaemia.
The most common, severe adverse reactions (≥5% Grade 3 or 4) were diarrhoea, nausea, vomiting, decreased appetite, fatigue, asthenia, neutropenia, neutrophil count decreased, anaemia and hypokalaemia. The most common serious adverse reactions (≥2%) were diarrhoea, nausea, vomiting and dehydration.
Adverse reactions seen with ONIVYDE pegylated liposomal which led to its permanent discontinuation occurred in 9.5 % of patients; the most frequent adverse reaction resulting in discontinuation was neutropenia.
Dose reductions of ONIVYDE pegylated liposomal due to adverse events (regardless of causality assessment), occurred in 52.4% of patients; the most frequent adverse events requiring dose reduction (≥5%) were diarrhoea, nausea, neutropenia and neutrophil count decreased.
ONIVYDE pegylated liposomal was withheld due to adverse events (regardless of causality assessment), in 1.9% of patients; the most frequent adverse events requiring interruption were hypersensitivity and infusion related reactions that occurred in 0.5% of patients.

ONIVYDE pegylated liposomal in combination with 5-fluorouracil and leucovorin:

The following adverse reactions related to the administration of ONIVYDE pegylated liposomal, were reported in 264 patients with metastatic adenocarcinoma of the pancreas treated after disease progression following gemcitabine-based therapy.,
The most common adverse reactions (incidence ≥ 20%) of ONIVYDE pegylated liposomal +5-FU/LV were: diarrhoea, nausea, vomiting, decreased appetite, neutropenia, fatigue, asthenia, anaemia, stomatitis and pyrexia. The most common serious adverse reactions (≥ 2%) of ONIVYDE pegylated liposomal therapy were diarrhoea, vomiting, febrile neutropenia, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.
The rates of adverse reactions leading to permanent treatment discontinuation were 11% for the ONIVYDE pegylated liposomal +5-FU/LV arm
The most frequently reported adverse reactions leading to discontinuation were infection and diarrhoea for ONIVYDE pegylated liposomal +5-FU/LV arm

Tabulated list of adverse reactions

The adverse reactions described in this section are derived from studies data and post-marketing experience of ONIVYDE pegylated liposomal.
The adverse reactions that may occur during treatment with ONIVYDE pegylated liposomal are summarised below and are presented by system organ class and frequency category (Table 4). 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 4: Adverse reactions reported in patients treated with ONIVYDE pegylated liposomal

SOC **Frequency***	**In combination with oxaliplatin/5-FU/LV (in NAPOLI-3)**	**In combination with 5-FU/LV (in NAPOLI-1 and in post-marketing experience)**
Infections and Infestations		
Common	Sepsis, Urinary tract infection, Candida infection, Nasopharyngitis	Septic shock, Sepsis, Pneumonia, Febrile neutropenia, Gastroenteritis, Oral candidiasis
Uncommon	Diverticulitis,Pneumonia, Anal abscess, Febrile infection, Gastroenteritis, Mucosal infection, Oral fungal infection, Clostridium difficile infection, Conjunctivitis, Furuncle, Herpes simplex, Laryngitis, Periodontitis, Rash pustular, Sinusitis, Tooth infection, Vulvovaginal mycotic infection	Biliary sepsis
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Uncommon	Peritumoural oedema	
Blood and lymphatic disorders		
Very common	Anaemia, Neutropenia, Thrombocytopenia	Neutropenia, Leukopenia, Anaemia, Thrombocytopenia
Common	Febrile neutropenia, Leukopenia, Lymphopenia	Lymphopenia
Uncommon	Pancytopenia, Haemolytic anaemia	
Immune system disorders		
Uncommon	Hypersensitivity	Hypersensitivity
Not known		Anaphylactic/Anaphylactoid reaction, Angioedema
Metabolism and nutrition disorders		
Very common	Hypokalaemia, Decreased appetite,	Hypokalaemia, Hypomagnesaemia, Dehydration, Decreased appetite
Common	Dehydration, Hyponatraemia, Hypophosphataemia, Hypomagnesaemia, Hypoalbuminaemia, Hypocalcaemia	Hypoglycaemia, Hyponatraemia, Hypophosphataemia
Uncommon	Electrolyte imbalance, Hypercalcaemia, Cell death, Hypochloraemia, Gout, Hyperglycaemia, Hyperkalaemia, Iron deficiency, Malnutrition	
Psychiatric disorders		
Common		Insomnia
Uncommon	Insomnia, Confusional state, Depression, Neurosis,	

Nervous system disorders		
Very common	Neuropathy peripheral, Dysgeusia, Paraesthesia	Dizziness
Common	Tremor, Neurotoxicity, Dysaesthesia, Cholinergic syndrome, Headache, Dizziness	Cholinergic syndrome, Dysgeusia
Uncommon	Seizure, Cerebral haemorrhage, Cerebral ischaemia, Ischaemic stroke, Anosmia, Ageusia, Balance disorder, Hypersomnia, Hypoaesthesia, Intellectual disability, Lethargy, Memory impairment, Presyncope, Syncope, Transient ischaemic attack	
Eye disorders		
Common	Vision blurred	
Uncommon	Eye irritation, Visual acuity reduced	
Ear and labyrinth disorders		
Uncommon	Vertigo	
Cardiac disorders		
Common	Tachycardia	Hypotension
Uncommon	Angina pectoris, Acute myocardial infarction, Palpitations	
Vascular disorders		
Common	Hypotension, Thromboembolic events	Pulmonary embolism, Thomboembolic events
Uncommon	Hypertension, Peripheral coldness, Haematoma, Phlebitis	
Respiratory, thoracic and mediastinal disorders		
Common	Pulmonary embolism, Hiccups, Dyspnoea, Epistaxis	Dyspnoea, Dysphonia
Uncommon	Oropharyngeal pain, Cough, Hyperoxia, Nasal inflammation, Atelectasis, Dysphonia, Pneumonitis	Hypoxia
Gastro-intestinal disorders		
Very common	Diarrhoea, Nausea, Vomiting, Abdominal pain/discomfort, Stomatitis	Diarrhoea, Vomiting, Nausea, Abdominal pain, Stomatitis
Common	Colitis, Enterocolitis, Constipation, Dry mouth, Flatulence, Abdominal distension, Dyspepsia, Gastrooesophageal reflux disease, Haemorrhoids, Dysphagia,	Colitis, Haemorrhoids
Uncommon	Gastrointestinal toxicity, Duodenal obstruction, Anal incontinence, Aphthous ulcer, Oral dysaesthesia, Oral pain, Tongue disorder, Anal fissure, Angular cheilitis, Dyschezia, Paraesthesia oral, Dental caries, Eructation, Gastric disorder, Gastritis, Gingival disorder, Gingival pain, Haematochezia, Hyperaesthesia teeth, Ileus paralytic, Lip swelling, Mouth ulceration, Oesophageal spasm, Periodontal disease, Rectal haemorrhage	Oesophagitis, Proctitis
Hepatobiliary disorders		
Common	Hyperbilirubinaemia	Hypoalbuminaemia
Uncommon	Cholangitis, Hepatitis toxic, Cholestasis, Hepatic cytolysis,	
Skin and subcutaneous tissue disorders		
Very common	Alopecia	Alopecia
Common	Dry skin, Palmar-plantar erythrodysaesthesia syndrome, Rash, Skin hyperpigmentation	Pruritus

Uncommon	Pruritus, Hyperhidrosis, Dermatitis bullous, Dermatitis exfoliative generalised, Erythema, Nail toxicity, Papule, Petechiae, Psoriasis, Sensitive skin, Skin exfoliation, Skin lesion, Telangiectasia, Urticaria	Urticaria, Rash, Nail discolouration
Not known		Erythema
Musculoskeletal and connective tissue disorders		
Common	Muscular weakness, Myalgia, Muscle spasms	
Uncommon	Arthralgia, Back pain, Bone pain, Pain in extremity, Polyarthritis	
Renal and urinary disorders		
Common	Acute kidney injury	Acute renal failure
Uncommon	Renal impairment, Renal failure, Dysuria, Proteinuria	
Reproductive system and breast disorders		
Uncommon	Vulvovaginal dryness	
General disorders and administration site conditions		
Very common	Asthenia, Mucosal inflammation	Pyrexia, Peripheral oedema, Mucosal inflammation, Asthenia
Common	Pyrexia, Oedema, Chills	Infusion related reaction, Oedema
Uncommon	Malaise, General physical health deterioration, Inflammation, Multiple organ dysfunction syndrome, Influenza like illness, Non-cardiac chest pain, Axillary pain, Chest pain, Hypothermia, Pain, Swelling face, Temperature intolerance, Xerosis	
Investigations		
Very common	Weight decreased	Weight decreased
Common	Transaminases (ALT and AST) increased, Blood alkaline phosphatase increased, Gamma-glutamyltransferase increased, Blood creatinine increased	Increased bilirubin, Transaminases (ALT and AST) increased, International normalised ratio increased
Uncommon	International normalised ratio increased, Protein total decreased, Creatinine renal clearance decreased, Electrocardiogram QT prolonged, Monocyte count increased, Troponin I increased	
Injury, poisoning and procedural complications		
Common	Infusion related reaction	

* Rare occurrence cannot be estimated from NAPOLI-1 study due to the small sample size.

Description of selected adverse reactions

Myelosuppression

ONIVYDE pegylated liposomal in combination with oxaliplatin, 5-fluorouracil and leucovorin:
Fatal events were febrile neutropenia or pancytopenia, each occurred in 0.3% of patients receiving NALIRIFOX arm.

ONIVYDE pegylated liposomal in combination with 5-fluorouracil and leucovorin:

Myelosuppression (neutropenia/leukopenia, thrombocytopenia and, anaemia) was more common in the ONIVYDE pegylated liposomal +5-FU/LV arm compared to the 5-FU/LV control arm.

Neutropenia/leukopenia

ONIVYDE pegylated liposomal in combination with oxaliplatin, 5-fluorouracil and leucovorin:
Grade 3 or 4 leukopenia occurred in 0.8% of patients receiving NALIRIFOX.
In NAPOLI-3, where ONIVYDE pegylated liposomal plus oxaliplatin/5-FU/LV (NALIRIFOX) was compared to gemcitabine plus nab-paclitaxel (Gem+NabP), safety data showed a higher incidence of neutropenia reported in the Gem+NabP arm. Grade 3 or 4 neutropenia, neutrophil count decreased and febrile neutropenia occurred in 14.1%, 9.7% and 1.9% (respectively) in patients receiving NALIRIFOX.

ONIVYDE pegylated liposomal in combination with 5-fluorouracil and leucovorin:
Neutropenia/leukopenia was the most notable important haematological toxicity. Grade 3 or higher neutropenia occurred more frequently in patients treated with ONIVYDE pegylated liposomal +5-FU/LV (27.4%) compared to patients treated with 5-FU/LV (1.5%). Neutropenic fever/sepsis appeared more frequently in the ONIVYDE pegylated liposomal +5-FU/LV combination arm [in 4 patients (3.4%)] compared to 5-FU/LV control arm [in 1 patient (0.7%)].
The median time to nadir for ≥ Grade 3 neutropenia is 23 (range 8-104) days post first dose of treatment with ONIVYDE pegylated liposomal.

Thrombocytopenia

ONIVYDE pegylated liposomal in combination with oxaliplatin, 5-fluorouracil and leucovorin:
Grade 3 or 4 thrombocytopenia occurred in 0.5% of patients receiving NALIRIFOX.

ONIVYDE pegylated liposomal in combination with 5-fluorouracil and leucovorin:
Grade 3 or higher thrombocytopenia occurred in 2.6% of patients treated with ONIVYDE pegylated liposomal +5-FU/LV and 0% in patients treated with 5-FU/LV.

Anaemia

ONIVYDE pegylated liposomal in combination with oxaliplatin, 5-fluorouracil and leucovorin:
Grade 3 or 4 anaemia occurred in 7.3% of patients receiving NALIRIFOX.

ONIVYDE pegylated liposomal in combination with 5-fluorouracil and leucovorin:
Grade 3 or higher anaemia occurred in 10.3% of patients treated with ONIVYDE pegylated liposomal +5-FU/LV and in 6.7% of patients treated with 5-FU/LV.

Acute renal failure

ONIVYDE pegylated liposomal in combination with oxaliplatin, 5-fluorouracil and leucovorin:
In NAPOLI-3, renal impairment occurred in 0.3% of patients and was of Grade 3 or 4, renal failure occurred with Grade 1 to 4 in 0.5% of patients, among them 0.3% was Grade 3 or 4, acute kidney injury occurred with Grade 1 to 4 in 1.1% of patients, among them 0.8% were of Grade 3 or 4 in patients receiving NALIRIFOX. Blood creatinine increased occurred with all Grade 1 to 4 in 1.4% of patients, among them, 0.3% was Grade 3 or 4, creatinine renal

clearance decreased occurred with Grade 1 or 2 in 0.3% of patients receiving NALIRIFOX. There was one case (0.3%) of renal failure with a fatal outcome in the NALIRIFOX arm.

ONIVYDE pegylated liposomal in combination with 5-fluorouracil and leucovorin:
In NAPOLI-1, 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 pegylated liposomal +5-FU/LV arm~~,~~

Diarrhoea and related adverse reactions
ONIVYDE pegylated liposomal in combination with oxaliplatin, 5-fluorouracil and leucovorin:
In NAPOLI-3, safety data showed a higher incidence of diarrhoea reported in the NALIRIFOX arm for all grades and for grade 3 or 4. Grade 1 to 4 diarrhoea occurred in 64.3% of patients and Grade 3 or 4 diarrhoea occurred in 19.5% of patients receiving NALIRIFOX arm. Cholinergic reaction manifestations such as rhinitis, rhinorrhoea, salivary hypersecretion, flushing, hot flush and lacrimation increased, were reported in patients receiving NALIRIFOX.

ONIVYDE pegylated liposomal in combination with 5-fluorouracil and leucovorin:
In NAPOLI-1, Grade 3 or Grade 4 diarrhoea occurred ~~(~~12.8%~~)~~ receiving ONIVYDE pegylated liposomal +5-FU/LV. For patients experiencing late diarrhoea, the median time to late diarrhoea onset was 8 days from the previous dose of ONIVYDE pegylated liposomal. Early onset diarrhoea, typically appearing ≤ 24 hours after dose administration, can occur and is usually transient. Early onset diarrhoea may also be accompanied by cholinergic symptoms that can include rhinitis, increased salivation, flushing, diaphoresis, bradycardia, miosis and hyperperistalsis that can induce abdominal cramping.

Early diarrhoea onset occurred in ~~(~~29.9%~~)~~ and cholinergic events occurred in ~~(~~3.4%~~)~~ receiving ONIVYDE pegylated liposomal +5-FU/LV.

Infusion reaction

ONIVYDE pegylated liposomal in combination with oxaliplatin, 5-fluorouracil and leucovorin:
In NAPOLI-3, Infusion related reaction occurred in 1.4% of patients receiving NALIRIFOX. All of them were mild or moderate (Grade 1 and 2).

ONIVYDE pegylated liposomal in combination with 5-fluorouracil and leucovorin:
In NAPOLI-1, acute infusion reactions were reported in in the ONIVYDE pegylated liposomal +5-FU/LV arm

Other special populations

Elderly

Overall, no major clinical differences in safety were reported between patients ≥ 65 years and patients < 65 years.

ONIVYDE pegylated liposomal in combination with oxaliplatin, 5-fluorouracil and leucovorin:
In NAPOLI-3, the median age was 65 years (range from 20 to 85), 50.1% of patients were at least 65 years of age with 6.9% of patients of 75 years or older. The safety data by age groups, were in line with the data of NALIRIFOX arm in the whole population.

ONIVYDE pegylated liposomal in combination with 5-fluorouracil and leucovorin:
In NAPOLI-1, a higher frequency of discontinuation was noted for patients between ≥ 65 years and < 65 years treated with ONIVYDE pegylated liposomal +5-FU/LV (14.8% vs 7.9% respectively) and in some cases the adverse reactions did not resolve. Grade 3 or higher and serious treatment emergent adverse reactions were more frequent in patients < 65 years (84.1% and 50.8%) compared to patients ≥ 65 years (68.5 % and 44.4%). 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) when treated with ONIVYDE pegylated liposomal +5-FU/LV in the pancreatic adenocarcinoma study.

Asian population

In NAPOLI-1, 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 pegylated liposomal +5-FU/LV, the incidence of ≥ Grade 3 neutropenia was higher among Asian patients [18 of 33 (55%)] compared to Caucasian patients [13 of 73 (18%)]. Neutropenic fever/neutropenic sepsis was reported in 6% of Asian patients compared to 1% of Caucasian patients. This is consistent with the population pharmacokinetic analysis that showed a lower exposure to irinotecan and a higher exposure to its active metabolite SN-38 in Asians than in Caucasians.

Patients with hepatic impairment

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.

Patients with UGT1A1 allele
Individuals who are 7/7 homozygous for the UGT1A1*28 allele are at increased risk for neutropenia from non-liposomal irinotecan. In NAPOLI-, the frequency of ≥ Grade 3 neutropenia in these patients [2 of 7 (28.6%)] was similar to the frequency in patients not homozygous for the UGT1A1*28 allele who received a starting dose of ONIVYDE pegylated liposomal of 70 mg/m^2 [30 of 110 (27.3%)] (see section 5.1). This observation was not evaluated in NAPOLI-3.

Underweight patients (body mass index < 18.5 kg/m^2)
In NAPOLI-1,-5 of 8 underweight patients experienced a grade 3 or 4 adverse reaction, mostly myelosuppression, while 7 of the 8 patients required dose modification such as dose delay, dose reduction or dose discontinuation (see section 4.4). This observation was not evaluated in NAPOLI-3.

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

In clinical trials, ONIVYDE pegylated liposomal 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 dose 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 pegylated liposomal. 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

Pharmacotherapeutic group: Topoisomerase 1 (TOP1) inhibitors. ATC Code: L01CE02

Mechanism of action

The active substance in ONIVYDE pegylated liposomal is irinotecan (topoisomerase I inhibitor) encapsulated in a lipid bilayer vesicle or liposome.

Irinotecan is a derivative of camptothecin. Camptothecins act as specific inhibitors of the enzyme DNA topoisomerase I. Irinotecan and its active metabolite SN-38 bind reversibly to the topoisomerase I-DNA complex and induce single-strand DNA lesions which block the DNA replication fork and are responsible for the cytotoxicity. Irinotecan is metabolised by carboxylesterase to SN-38. SN-38 is approximately 1,000 times as potent as irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumour cell lines.

Pharmacodynamic effects

In animal models, ONIVYDE pegylated liposomal has been shown to extend plasma levels of irinotecan and prolong the exposure to the active metabolite SN-38 at the site of the tumour.

Clinical efficacy and safety

NAPOLI-3:

The safety and efficacy of ONIVYDE pegylated liposomal in combination with oxaliplatin, 5-fluorouracil and leucovorin (NALIRIFOX) was evaluated in NAPOLI-3, a randomised, multicenter, open-label, active-controlled study that included 770 patients with metastatic adenocarcinoma of the pancreas who had not previously received chemotherapy in the metastatic setting. Randomisation was stratified by region, liver metastases and ECOG

performance status. Patients were randomized (1:1) to receive one of the following treatment arms:

NALIRIFOX: ONIVYDE pegylated liposomal 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 1000 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 pegylated liposomal at the same dose (50 mg/m^2 ONIVYDE pegylated liposomal) and were closely monitored for safety.

Treatment continued until RECIST V1.1 defined disease progression or unacceptable toxicity. Tumor status assessments were conducted at baseline and every 8 weeks thereafter as assessed by the investigator according to RECIST v1.1.

The main efficacy outcome measures were Overall Survival (OS), Progression-Free Survival (PFS) and Objective Response Rate (ORR).

Baseline demographics and patient characteristics were: median age of 65 years (range: 20-85); 50% age 65 or older; 56% male; 83% White; 5% Asian; 3% Black or African American; ECOG performance status was 0 in 43% or 1 in 57% of patients; 87% liver metastases.

NAPOLI-3 demonstrated a statistically significant improvement in OS and PFS for the NALIRIFOX arm over Gem+NabP arm as per original strata definition in the statistical analysis plan. Median OS was 11.1 months (95% CI: 10.0, 12.1; HR 0.84 (95% CI: 0.71, 0.99); p=0.04) for the NALIRIFOX arm and 9.2 months (95% CI: 8.3, 10.6) for the Gem+NabP arm at the final analysis. Results from an updated OS analysis are summarized in Table 5 and Figure 1 (OS).

Table 5: Efficacy Results from NAPOLI-3 clinical study

	NALIRIFOX (N=383)	**Gem+NabP** (N=387**)**
Updated Overall Survival, cut-off = 03 October 2023		
Number of Deaths, n (%)	328 (85.6)	345 (89.1)
Median Overall Survival (months)	11.1	9.2
(95% CI)	(10.0, 12.1)	(8.3, 10.6)
Hazard Ratio (95% CI) *	0.85 (0.73, 0.99)	
Progression-Free Survival, cut-off = 23 July 2022**		
Death or Progression, n (%)	249 (65)	259 (67)
Median Progression-Free Survival (months)	7.4	5.6
(95% CI)	(6.0, 7.7)	(5.3, 5.8)
Hazard Ratio (95% CI)*	0.70 (0.59, 0.84)	

	NALIRIFOX (N=383)	**Gem+NabP** (N=387**)**
p-value †	0.0001	
Objective Response Rate, cut-off = 23 July 2022		
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 pegylated liposomal +oxaliplatin/5-fluorouracil/leucovorin; Gem+NabP=gemcitabine+nab-paclitaxel

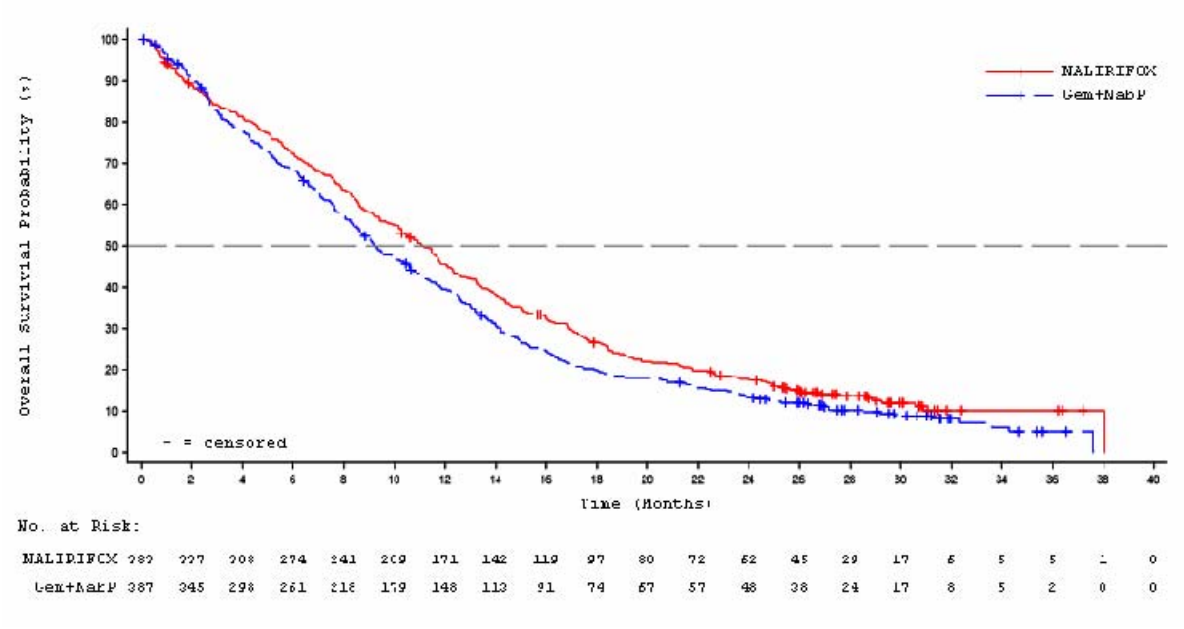
* Based on the stratified Cox proportional hazard model by baseline ECOG performance status, region (North America, East Asia and Rest of the World) and liver metastases

** Patients were censored when initiated subsequent anti-cancer therapy or withdrawal of study consent or lost to FU or if 2 consecutive tumour assessments were missed and followed by progression or death

† Based on stratified log-rank test.

Abbreviations: CR=complete response, PR=partial response; CI=confidence interval

Figure 1: Kaplan-Meier Curve for Updated Overall Survival, cut-off = 03 October 2023 in NAPOLI-3



NAPOLI-1:

The safety and efficacy of ONIVYDE pegylated liposomal were investigated in a multinational, randomised, open label, controlled clinical study (NAPOLI–1) that tested two treatment regimens for patients with metastatic pancreatic adenocarcinoma who had documented disease progression after gemcitabine or gemcitabine-containing therapy. The study was designed to assess the clinical efficacy and safety of ONIVYDE pegylated

liposomal monotherapy or ONIVYDE pegylated liposomal+5-FU/LV compared to an active control arm of 5-FU/LV.

Patients randomised to ONIVYDE pegylated liposomal+5-FU/LV received ONIVYDE pegylated liposomal at 70 mg/m^2 as an intravenous infusion over 90 minutes, followed by LV 400 mg/m^2 intravenously over 30 minutes, followed by 5-FU 2,400 mg/m^2 intravenously over 46 hours, administered every 2 weeks. Patients homozygous for the UGT1A1*28 allele were given a lower initial dose of ONIVYDE pegylated liposomal (see section 4.2). Patients randomised to 5-FU/LV received leucovorin 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 randomised to ONIVYDE pegylated liposomal monotherapy received 100 mg/m^2 as an intravenous infusion over 90 minutes every 3 weeks.

Key eligibility criteria for patients with metastatic adenocarcinoma of the pancreas in the NAPOLI-1 clinical study were Karnofsky Performance Status (KPS) $\geq$ 70, normal bilirubin level, transaminase levels $\leq$ 2.5 times the ULN or $\leq$ 5 times the ULN for patients with liver metastases and albumin $\geq$ 3.0 g/dl.

A total of 417 patients were randomised to the ONIVYDE pegylated liposomal+5-FU/LV arm (N=117), ONIVYDE pegylated liposomal monotherapy arm (N=151) and 5-FU/LV arm (N=149). Patient demographic and entry disease characteristics were well balanced between study arms.

In the intent to treat (all randomised) population, the median age was 63 years (range 31-87 years), 57 % were males, and 61% were Caucasian and 33% were Asian. Mean baseline albumin level was 3.6 g/dl, and baseline KPS was 90-100 in 55% of patients. Disease characteristics included 68% of patients with liver metastases and 31% with lung metastases; 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.

Patients received treatment until disease progression or unacceptable toxicity. The primary outcome measure was Overall survival (OS). Additional outcome measures included Progression free survival (PFS) and Objective response rate (ORR). Results are shown in Table 6. Overall survival is illustrated in Figure 2.

Table 6: Efficacy results from NAPOLI-1 clinical study

	ONIVYDE pegylated liposomal+5-FU/LV (N= 117)	**5-FU/LV (N= 119)**
Overall survival[1]		
Number of deaths, n (%)	**75 (64)**	**80 (67)**
Median OS (months)	6.1	4.2
(95% Confidence Interval(CI))	(4.8, 8.9)	(3.3, 5.3)

	ONIVYDE pegylated liposomal+5-FU/LV (N= 117)	**5-FU/LV (N= 119)**
Hazard Ratio (95% CI)[3]	0.67 (0.49-0.92)	
p-value[4]	0.0122	
Progression-free survival[1,2]		
Death or progression, n (%)	83 (71)	92 (77)
Median PFS (months)	3.1	1.5
(95% CI)	(2.7, 4.2)	(1.4, 1.8)
Hazard Ratio (95% CI)[3]	0.56 (0.41-0.75)	
p-value[4]	0.0001	
Objective response rate[2]		
N	19	1
ORR (%)	16.2	0.8
95% CI of Rate[5]	9.6, 22.9	0.0, 2.5
Rate Difference (95% CI)[5]	15.4 (8.5, 22.3)	
p-value[6]	< 0.0001	

1 Median is the Kaplan-Meier estimate of the median survival time
2 Per RECIST guidelines, v 1.1.
3 Cox model analysis
4 Unstratified log-rank test
5 Based on Normal approximation
6 Fisher's exact test

Abbreviations: 5-FU/LV=5-fluorouracil/leucovorin; CI=confidence interval

Figure 2: Kaplan-Meier Curve for Overall survival in NAPOLI-1

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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with ONIVYDE pegylated liposomal in all subsets of the paediatric population in treatment of pancreatic cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Liposome encapsulation of irinotecan extends circulation and limits distribution relative to those of the non-liposomal irinotecan.

The plasma pharmacokinetics of total irinotecan and total SN-38 were evaluated in patients with cancer who received ONIVYDE pegylated liposomal as a single agent or as part of combination chemotherapy, at doses between 35 and 155 mg/m^2 in 1058 patients with cancer using population pharmacokinetic analysis. The pharmacokinetic parameters of total irinotecan and SN-38 analytes, following the administration of ONIVYDE pegylated liposomal 70 mg/m^2 as a single agent or as part of combination chemotherapy and 50 mg/m^2 in the NALIRIFOX regimen (ONIVYDE pegylated liposomal/oxaliplatin/5-FU/LV) are presented in Table 7.

Table 7: Summary of geometric Mean (geometric CV) Total Irinotecan and Total SN-38

Starting dose (mg/m^2)	Descriptive Statistics	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	360	360	360	360
	Geometric Mean	25.1	37.8	1.93	2.09	12.1
	Geometric CV (%)	18.5	73.6	14	42.1	46.6
70**	N	116	116	116	116	116

	Geometric Mean	29.0	46.6	1.91	2.50	14.5
	Geometric CV (%)	17.6	60.3	8.4	57.3	45.0

AUC_{SS}: Area under the plasma concentration curve at steady-state per two weeks

$t_{1/2}$: Terminal elimination half-life
Cmax = maximum plasma concentration
CV = coefficient of variation
* ONIVYDE pegylated liposomal/oxaliplatin/5-FU/leucovorin (NAPOLI-3)
** ONIVYDE pegylated liposomal/5-FU/leucovorin (NAPOLI-1)

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 (138 l/m^2). The volume of distribution of ONIVYDE pegylated liposomal is 4 L (obtained from population pharmacokinetic analysis), which suggests that ONIVYDE pegylated liposomal is largely confined to vascular fluid.
The plasma protein binding of ONIVYDE pegylated liposomal is negligible (< 0.44% of total irinotecan in ONIVYDE pegylated liposomal). 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%).

Biotransformation

Irinotecan released from liposome encapsulation follows a similar metabolic pathway reported with non-liposomal 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. In the population pharmacokinetic analysis, there was no significant association between UGT1A1*28 polymorphism (7/7 homozygous (8%) vs non 7/7 homozygous) and SN-38 clearance.

Elimination

The disposition of ONIVYDE pegylated liposomal and non-liposomal irinotecan has not been fully elucidated in humans.
The urinary excretion of non-liposomal irinotecan is 11% to 20%; SN38 < 1%; and SN38 glucuronide is 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN38 and SN38 glucuronide) over a period of 48 hours following administration of non-liposomal irinotecan in two patients ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2).

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 (see sections 4.2 and 4.4).

Hepatic impairment

No dedicated pharmacokinetic study has been conducted in patients with hepatic impairment. In a population pharmacokinetic analysis, increased bilirubin level was associated with lower SN-38 clearance. Bilirubin level of 1.14 mg/dL (95th percentile of the overall population) leads to a 32% increase of SN-38 AUC in comparison to median bilirubin level of 0.44 mg/dL (of the 1055 patients evaluated in the model, 54 had bilirubin levels ≥ 1.14 mg/dL). No data are available in patients with bilirubin >2.8 mg/dL). There was no effect of elevated ALT/AST concentrations on total SN-38 concentrations. No data are available in patients with total bilirubin more than 2 times the ULN.

Other special populations

Age and gender
The population pharmacokinetic analysis in patients aged 20~~8~~ to 87 years, of whom 11% in previous studies and 6.9% in NAPOLI-3 were ≥75 years, suggests that age had no clinically meaningful effect on the exposure to irinotecan and SN-38.

Gender was found as a significant covariate in the population PK analysis with an irinotecan AUC increase of 28% and a clinically meaningful SN-38 AUC increase of 32% in female, when not adjusted for any other covariate.

Ethnicity
Population pharmacokinetic analysis shows that irinotecan AUC is 32% lower, being clinically meaningful, in participants of Asian ethnicity than in participants of other ethnicities.

Pharmacokinetic/pharmacodynamic relationship

NAPOLI-3:

In the exposure-safety analysis focusing on the data of 360 subjects included in NAPOLI-3 study and treated with 50 mg/m² of ONIVYDE pegylated liposomal in combination with 5-FU, LV and oxaliplatin, probability of diarrhoea Grade 3 and higher or neutropenia Grade 3 or higher appeared to increase with increasing exposures of both irinotecan and SN-38. Exposure-efficacy relationship was not found to be statistically significant.

NAPOLI-1:

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 NAPOLI-1, higher plasma exposures of total irinotecan and SN-38 for patients in the ONIVYDE pegylated liposomal +5-FU/LV treatment arm were associated with longer OS and PFS as well as with higher ORR (objective response rate).

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 haematologic 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 pegylated liposomal once every 3 weeks for 18 weeks was 155 mg/m^2.

In safety pharmacology studies in dogs, ONIVYDE pegylated liposomal had no effect on cardiovascular, haemodynamic, electrocardiographic, or respiratory parameters at doses up to 18 mg/kg or 360 mg/m². 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 pegylated liposomal. 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 pegylated liposomal. For non-liposomal irinotecan, in rats treated once a week during 13 weeks at the maximum dose of 150 mg/m², 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 pegylated liposomal.

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 20 mg/kg and 0.4 mg/kg, respectively.These effects were reversible upon cessation of treatment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liposome forming lipids

1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)

Cholesterol

N-(carbonyl-methoxypolyethylene
glycol-2000)-1, 2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE)

Other excipients

Sucrose octasulphate

2- [4- (2-Hydroxyethyl)piperazin-1-yl] ethanesulfonic acid (HEPES buffer)

Sodium chloride

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

3 years.

After dilution

Chemical and physical stability for the diluted dispersion for infusion has been demonstrated at 15-25°C for up to 6 hours or in the refrigerator (2ºC-8ºC) for no more than 24 hours.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

Type I glass vial with a grey chlorobutyl stopper and an aluminium seal with a flip-off cap, containing 10 ml of concentrate.

Each pack contains one vial.

6.6 Special precautions for disposal

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

Preparation of the dispersion and administration

ONIVYDE pegylated liposomal 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% glucose solution for injection or sodium chloride 9 mg/ml (0.9%) solution for injection to prepare a dispersion of the appropriate dose of ONIVYDE pegylated liposomal diluted to a final volume of 500 ml. Mix the diluted dispersion by gentle inversion. The diluted dispersion is clear to slightly white to slightly opalescent and free from visible particles.

For first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas, ONIVYDE pegylated liposomal should be administered before oxaliplatin, followed by LV, followed by 5-FU. For treatment of metastatic adenocarcinoma of the pancreas in adult patients who have progressed following gemcitabine based therapy, ONIVYDE pegylated liposomal should be administered before LV followed by 5-FU. ONIVYDE pegylated liposomal must not be administered as a bolus injection or an undiluted dispersion.

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

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 sodium chloride 9 mg/ml (0.9%) solution for injection and/or sterile water and applications of ice are recommended.

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

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

7 MARKETING AUTHORISATION HOLDER

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