EU Risk Management Plan for Onivyde® Pegylated Liposomal

(liposomal irinotecan)

RMP version to be assessed as part of this application:

RMP version number: 5.0
Data lock point: 22 April 2023
Date of final sign off: 04 March 2024

Rationale for submitting an updated RMP:

This RMP is submitted in the frame of a type II variation for the addition of a new indication of irinotecan liposome injection (Onivyde® Pegylated Liposomal) for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas, in combination with oxaliplatin, 5-fluorouracil (5-FU) and leucovorin (LV).

Summary of significant changes in this RMP:

Addition of new indication and dosage regimen (Part I), update of epidemiology of the indication and target population (Part II-Module SI), update of exposure data from clinical trials (Part II-Module SIII) and post-authorisation exposure (Part II-Module SV) as of 22 April 2023.

Other RMP Versions under evaluation: Not Applicable

Details of currently approved RMP:
RMP version number: 4.0
Approved with procedure EMEA/H/C/PSUSA/00010534/202110
Date of approval (opinion date): 23 June 2022

QPPV name: **Dr. Fairouz SMAIL-AOUDIA**

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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List of In-Text Tables

Abbreviations

5-FU	5-fluorouracil
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ASR	Age-standardized rate
ATC code	Anatomical Therapeutic Chemical code
AUC	Area Under the Plasma Concentration Time Curve
CA	Canada
C_{max}	Maximum Plasma Concentration
COPD	Chronic Obstructive Pulmonary Disease
DHPC	Direct Healthcare Professional Communication
DNA	Deoxyribonucleic Acid
e.g.	For Example
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EPAR	European Public Assessment Report
et al	And Others
EU	European Union
FOLFIRINOX	5-FU+Irinotecan+Oxalipaltin
GI	Gastrointestinal
HCL	Hydrochloride
i.e.	that is
ILD	Interstitial lung disease
INN	International Nonproprietary Name
IV	Intravenous
kg	Kilogram
LV	Leucovorin
m	Meter
m^2	square Meter
MAA	Marketing Authorisation Application
max	maximum
mg	Milligram
ml	Millilitre

MTD	Maximum Tolerated Dose
Nab-paclitaxel	albumin-bound paclitaxel
N, n	Number
NAPOLI	NAnoliPOsomaL Irinotecan
NCCN	National Comprehensive Cancer Network
NOAEL	No Adverse Event Limit
PDAC	pancreatic ductal adenocarcinoma
PK	Pharmacokinetic
PS	performance status
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TEAE	Treatment Emergent Adverse Event
ULN	upper limit of normal
USA	United States of America

Part I: Product Overview

Table 1. Product Overview

Active Substance(s) (International Nonproprietary Name (INN) or generic name)	Liposomal irinotecan
Pharmacotherapeutic group(s) Anatomical Therapeutic Chemical code (ATC Code)	L01CE02
Name of Marketing Authorization Holder:	Les Laboratoires Servier
Medicinal products to which this RMP refers	Onivyde pegylated liposomal
Invented name(s) in the European Economic Area (EEA):	Onivyde pegylated liposomal
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class** The active substance in Onivyde pegylated liposomal (hereinafter referred as ONIVYDE) is irinotecan (topoisomerase I inhibitor) encapsulated in a lipid bilayer vesicle or liposome.
	Summary of mode of action Irinotecan is a derivative of camptothecin. Camptothecins act as specific inhibitors of the enzyme Deoxyribonucleic Acid (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.
	Important information about its composition ONIVYDE differs from standard irinotecan products as it is a liposomal formulation. The liposome is a small, unilamellar, lipid bilayer vesicle approximately 110 nm in diameter that encapsulates an aqueous space containing irinotecan in a gelated or precipitated state as the sucrosofate salt. The lipid membrane is composed of phosphatidylcholine, cholesterol, and a polyethyleneglycolderivatised-phosphatidyl-ethanolamine in the amount of approximately one polyethyleneglycol molecule for 200 phospholipid molecules.
Hyperlink to the Product Information	Module 1.3.1
Indication in the EEA	ONIVYDE is indicated in: – First-line treatment of adult patients with metastatic adenocarcinoma of the pancreas, in combination with oxaliplatin, 5-fluorouracil (5-FU) and leucovorin (LV). – Treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil (5-FU) and leucovorin (LV), in adult patients who have progressed following gemcitabine-based therapy.

Table 1. Product Overview

Dosage in the EEA	ONIVYDE should not be administered as a single agent. **ONIVYDE in combination with oxaliplatin, 5-fluorouracil and leucovorin:** ONIVYDE, oxaliplatin, LV and 5-FU should be administered sequentially. The recommended dose of ONIVYDE is 50 mg/m² intravenously (i.v.) over 90 minutes, followed by oxaliplatin 60 Milligram per square Meter (mg/m²) i.v. over 120 minutes, followed by LV 400 mg/m^2 i.v. over 30 minutes, followed by 5-FU 2,400 mg/m^2 i.v. over 46 hours, administered every 2 weeks. The recommended starting dose of ONIVYDE in patients known to be homozygous for UGT1A1*28 allele is unchanged and remains 50 mg/m^2 administered intravenously over 90 minutes (see sections 5.1, and 5.2). **ONIVYDE in combination with 5-fluorouracil and leucovorin:** ONIVYDE, leucovorin and 5-fluorouracil 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. A reduced starting dose of ONIVYDE 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 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 5-HT_3 antagonist (or other antiemetic) at least 30 minutes prior to ONIVYDE infusion. For specific dosing recommendations and additional details, please see Module 1.3.1
Pharmaceutical form and strengths	Concentrate for dispersion for infusion. One 10 Millilitre (ml) vial of concentrate contains the equivalent of 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). White to slightly yellow opaque isotonic liposomal dispersion. The concentrate has a pH of 7.2 and an osmolality of 295 mOsm/ Kilogram (kg).
Is/will the product be subject to additional monitoring in the European Union EU?	No

Part II: Safety Specification

Part II: Module SI - Epidemiology of the Indication(s) and Target Population

Table SI. Epidemiology for metastatic adenocarcinoma of the pancreas

Incidence	Pancreatic cancer is the seventh most common cause of cancer worldwide and in 2020 there were almost as many deaths as new diagnoses (Sung And Others (et al.) 2021). There were an estimated 495,773 diagnoses of pancreatic cancer in 2020 (the latest available date), making it the 12th most commonly diagnosed cancer, worldwide (International Agency for Research on Cancer. Cancer today 2020). In Europe, the estimated number (N) of new cases was 140,116, equivalent to an Age-Standardized incidence rate (ASR) of 7.8 new cases per 100,000 inhabitants according to GLOBOCAN 2020 estimates (Globocan 2020. Global Cancer Observatory (iarc.fr). 2020). In Europe, the ASR is the highest in the Western part especially in Austria, France and Germany, ranging between 8.6 to 9/100,000 persons in 2020. Over 90% of pancreatic cancers are adenocarcinomas with the most common type being pancreatic ductal adenocarcinoma (PDAC) (Ducreux et al. 2015; Tempero et al. 2021).
Prevalence	Pancreatic cancer ranks 21st in terms of 5-year prevalence in Europe with 103,072 patients in 2020 (Globocan 2020. Global Cancer Observatory (iarc.fr). 2020)
Demographics of the population in the authorised indication	Pancreatic cancer usually affects older adults over the age of 65 years. Primarily a disease of the elderly, the median age at diagnosis is 72 years and 68% of patients are 65 years of age or older at diagnosis. Cancer of the pancreas may be linked to smoking, drinking too much alcohol, diabetes, obesity and chronic inflammation of the pancreas (Wild CP et al. 2020). The 2017 Global Burden of Disease Study showed higher incidence in men than women, as well as higher incidence in high-income countries (GBD 2017 Pancreatic Cancer Collaborators 2019).
Main existing treatment options	Although substantial progress has been made in understanding of pancreatic cancer biology and in the development of more effective chemotherapeutics generally, for patients with metastatic pancreatic adenocarcinoma, there are currently few treatment options. Gemcitabine monotherapy has been the standard of care for patients with metastatic pancreatic cancer since 1997 when it was shown to demonstrate significant survival benefit over 5-FU (Burris et al. 1997). Since then, combination therapy with gemcitabine plus erlotinib was shown to increase median survival by 2 weeks (Moore et al. 2007) and more recently, the gemcitabine plus albumin-bound paclitaxel (nab-paclitaxel) combination was shown to increase median survival by 1.8 months, with increased overall survival at 1 and 2 years (Hoff et al. 2013). The current National Comprehensive Cancer Network (NCCN) recommendations and the European Society for Medical Oncology (ESMO) guidelines suggest chemotherapy combinations for patients with good performance status (PS) (that is (i.e.), Eastern Cooperative Oncology Group performance status [ECOG PS] of 0 or 1), good pain management, patent biliary stent, and adequate nutritional intake; these combinations include 5-FU+Irinotecan+Oxalipaltin (FOLFIRINOX) and gemcitabine combined with nab-paclitaxel. The only recommended option for patients with poor performance status in both guidelines is gemcitabine monotherapy or best supportive care in those with worse PS (Ducreux et al. 2015; ESMO Guidelines Committee. 2019; Tempero et al. 2021). After failure of first line therapy, the options are even more limited. Liposomal irinotecan/5-FU and leucovorin was recommended for second line treatment in the ESMO's and NCCN's most recent guidelines for fit patients after a phase 3 randomized trial (NAPOLI 1) showed survival advantage over 5-FU and leucovorin (ESMO Guidelines Committee. 2019; Tempero et al. 2021).
Natural history of the indicated condition in the population, including mortality and morbidity	The majority of patients present at a late stage in the disease course, with only approximately 15-20% with potentially resectable disease and the remaining 30% and 50% having locally-advanced unresectable and metastatic disease, respectively (Mizrahi et al. 2020) . About 60%-90% of resected patients will develop locally recurrent or metastatic disease despite surgery and adjuvant treatment (Taieb et al. 2020). Metastatic pancreatic adenocarcinoma portends a very poor prognosis. There were an estimated 466,000 deaths attributed to the disease worldwide in 2020

Table SI. Epidemiology for metastatic adenocarcinoma of the pancreas

	and in Europe, it is the fourth leading cause of cancer death, responsible for 132,134 estimated deaths in 2020 (Globocan 2020. Global Cancer Observatory (iarc.fr). 2020). Globally, the annual number of cases and deaths related to pancreatic cancer, which has increased more than two-fold since the 1990s, is expected to rise further by almost 80% by 2040 (to 815,276 and 777,423, respectively (Frampton 2020). Most patients with pancreatic cancer present with nonspecific symptoms such as decreased appetite, abdominal pain, indigestion and change in bowel habit. Most tumors arise at the head of the pancreas, presenting then with biliary obstruction leading to choluria, jaundice, fatigue and appetite loss, but often appearing late, when the tumor is advanced. These unspecific symptoms lead to a late diagnosis, often at an advanced stage with disease that is not amenable to curative surgery. No effective screening exists to date. The 5-year survival rate approached 10% in all pancreatic cancer patients for the first time in 2020, compared with 5.26% in 2000 (Park et al. 2021). While improvement in survival rates of unresectable advanced disease has been minimal over recent decades. The 5-y survival rate can reach only 1% in the case of metastatic disease, with an overall survival of less than 1 year in this sub-population despite treatment. The principal reasons for the high mortality rate relative to other cancers include: late stage at presentation owing to vague symptom profile, rapid metastases, resistance to radio and chemotherapy due to hypocellularity and dense stroma surrounding the tumor (Krishnan 2023)and the limited treatment options available for the disease.
Important co-morbidities	Comorbidities are consistent with the risk factor profile of the disease and the advanced age of the majority of patients. In an analysis of 130,728 U.S. Medicare patients (> 65 years of age) with a hospitalisation event for pancreatic cancer, primary comorbidities (with prevalence >10%) included: hypertension (59%), diabetes (34%), malnutrition (18%), Chronic Obstructive Pulmonary Disease COPD (13%), and atherosclerosis (21%)) (Wang et al. 2014). Additionally, 58% were also reported to have “other cancer”, likely indicative of metastasis rather than additional primary malignancy.

Part II: Module SII – Non-Clinical Part of the Safety Specification

Table SII. Overview of Non-Clinical Studies

Key safety findings (from non-clinical studies)	Relevance to human usage
Toxicity	
Single-Dose Toxicity Acute single dose toxicity studies were conducted in ICR mice (Study No. PEP02-NCG-Tx-003), (Crl: CD (SD) fSPF rats (Study No. PEP020NC-N-Tx-004), Sprague-Dawley rats (Study No. PEP02-NC-G-Tx-002), and Beagle dogs (Study No. PEP02-NC-G-Tx-007). The Maximum Tolerated Dose (MTD) after single intravenous (IV) dose in dogs was 15 mg/kg (300 mg/m^2) and the highest non-lethal dose in rats was 200 mg/kg (1200 mg/m^2). The acute toxic effects of both ONIVYDE and non-liposomal irinotecan were gastrointestinal (GI) changes and effects on the white blood cell population in the form of leukocytopenia. Therefore, the key target organs of toxicity are the gastrointestinal tract and the hematologic system.	The toxicology profile of non-liposomal irinotecan has been well characterised since the originator product was developed. The primary purpose of the non-clinical toxicology study program of ONIVYDE was to examine a difference in the profile due to liposome encapsulation and to determine the effect of a marked increase in systemic exposure to the active metabolite, SN-38, with the liposomal (encapsulated) irinotecan compared to non-liposomal irinotecan. The nonclinical toxicity studies show that, like non-liposomal irinotecan, the acute toxic effects of ONIVYDE expected in humans would be gastrointestinal, notably diarrhoea, and haematological toxicities, notably leukocytopenia, neutropenia, and anaemia. No additional safety concerns were raised in the non-clinical program due to liposomal encapsulation of irinotecan.

Table SII. Overview of Non-Clinical Studies

Key safety findings (from non-clinical studies)	Relevance to human usage
Repeat-Dose Toxicity Repeat dose toxicity studies were performed over 4 and 18 weeks in rats (Study No. PEP02NC-G-Tx006 and PEP02-NC-G-Tx-010) and dogs (Study No. PEP02-NC-G-Tx-009 and PEP02-NC-G-Tx-011). Principal treatment related effects of ONIVYDE in rats and dogs were related to gastrointestinal toxicity. Leukocytopenia was also noted. The No Adverse Event Limit (NOAEL) in the 18-week rat toxicity study (Study PEP02NC-G-Tx-010) was 30 mg/kg (180 mg/m2) for ONIVYDE and up to 340.5 µmol/kg phospholipid for the empty liposome control article corresponding to~6.3x higher phospholipid dose levels than at the NOAEL. Systemic exposure Area Under the Plasma Concentration Time Curve (AUC) for irinotecan at the NOAEL is 13.4x above the expected human exposure for an 80 mg/m2 dose. The NOAEL in the 18-week dog toxicity study (Study PEP02-NC-G-Tx-011 (1006-2162)) was 9 mg/kg (180 mg/m2) for ONIVYDE and 60 µmol/kg phospholipid for the empty liposome control article corresponding to 4x higher phospholipid dose levels than at the NOAEL. Systemic exposure (AUC) for irinotecan at the NOAEL is 1.6x above the expected human exposure for an 80 mg/m2 dose. Changes of the liver, thymus, and spleen weight were observed in rats and dogs and were reversible during the recovery period. Clinical chemistry indicative of changes in liver function were not affected by ONIVYDE in any of these studies. Furthermore, accumulation of foamy histiocytes, not always reversed during the recovery period, were observed in a variety of tissues in rats and dogs, particularly in dog spleens and lungs. In dogs treated with either ONIVYDE or non-liposomal irinotecan at 16 mg/kg, atrophy/necrosis of lymphoid tissues including spleen, lymph nodes and Peyer´s patches, and hepatic/splenic extramedullary haematopoiesis, was found.	

Table SII. Overview of Non-Clinical Studies

Key safety findings (from non-clinical studies)	Relevance to human usage
Genotoxicity, carcinogenicity, and reproductive and developmental toxicity No genotoxicity studies have been performed with ONIVYDE. Non-liposomal irinotecan and SN-38 were devoid of any mutagenic potential in the Ames test. However, non-liposomal irinotecan and SN-38 were genotoxic in the chromosomal aberration test in CHO (chromosome aberrations in Chinese hamster ovary) cells in vitro, and in the micronucleus test in mice in vivo.). No long-term carcinogenicity studies were conducted either with ONIVYDE or non-liposomal irinotecan. Studies in rats exposed to non-liposomal irinotecan doses that produced irinotecan Maximum Plasma Concentration (C_{max}) and AUC about 7.0 times and 1.3 times the respective values in patients administered 125 mg/m^2 weekly, showed a significant dose-dependent trend for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas. Effects on fertility and development have also been demonstrated in animal studies. Non-liposomal irinotecan was embryotoxic and teratogenic at doses below the human therapeutic dose in animal studies.	Due to its mechanism of action on DNA, ONIVYDE is potentially genotoxic, carcinogenic and teratogenic.
Safety pharmacology	
General Safety Pharmacology Cardiovascular system, [including potential effect on the QT interval prolongation] nervous system The safety pharmacology of non-liposomal irinotecan is well-established. No new renal, central and autonomic nervous systems, or gastrointestinal safety studies were conducted for ONIVYDE. In male and female beagle dogs, single intravenous infusions of ONIVYDE at doses up to 21 mg/kg (420 mg/m^2) had no effects on cardiovascular, haemodynamic, electrocardiographic, or respiratory parameters, or body temperature (Study 20036143). Central nervous system related endpoints were evaluated in course of the 6-cycle, 18-week repeated dose toxicity study with ONIVYDE in rats (Study PEP02-NC-G-Tx-010 (1005- 3071)). Findings like tremors, uncoordinated gait, walking on tips of toes, salivation and gnawing on cage wire were observed only in the non-liposomal irinotecan group at 75 mg/kg (450 mg/m^2). This is consistent with the known safety pharmacology of, non-liposomal irinotecan, and its active metabolite, SN-38. Doses of ONIVYDE at up to 190 mg/kg (1140 mg/m^2) did not produce CNS-related signs in this study. In the male Long Evans rat distribution study (Study PEP02-NC-N-PK-007) data showed that after i.v. administration of ONIVYDE (10 mg/kg) maximal radioactivity concentrations of 3.3 µg equiv irinotecan/g tissue were observed in brain tissues at the end of infusion. Radioactivity level in brain areas corresponded to ~1% of plasma levels at all measurable time points.	There are no new safety pharmacology findings relevant to clinical use of ONIVYDE.

Table SII. Overview of Non-Clinical Studies

Key safety findings (from non-clinical studies)	Relevance to human usage
Pharmacodynamic Drug Interactions The potential for pharmacodynamic drug interactions has not been investigated for ONIVYDE in non-clinical studies.	Clinical pharmacodynamic interactions between irinotecan and co-administered medicinal products 5-fluorouracil/leucovorin are known. There is a potential for pharmacokinetic drug interactions in humans when ONIVYDE is co-administered with strong CYP3A4 inducers or inhibitors or UGT1A1 inhibitors. Known irinotecan pharmacokinetic drug interactions are potentially applicable to ONIVYDE.
Pharmacokinetic (PK) Drug Interactions No new non-clinical studies investigating potential pharmacokinetic drug interactions have been performed with ONIVYDE. However, non-liposomal irinotecan and its active metabolite SN-38 are metabolised via CYP3A4 and diphosphate-glucuronosyl transferase, respectively. Co-administration of non-liposomal irinotecan with inhibitors of CYP3A4 or UGT1A1 may increase systemic exposure while co-administration of irinotecan with CYP3A4 inducers may reduce systemic exposure.	

Part II: Module SIII – Clinical Trial Exposure

Brief Overview of Development

Irinotecan is a topoisomerase I inhibitor that was first approved in Europe in 1995 (Campto®). Several generic forms of Campto® now exist. Non-liposomal irinotecan is approved as first-line or second-line therapy in patients with advanced or metastatic colorectal cancer (either alone or in combination) and has been used for or is currently undergoing investigation in lung, gastric, cervical, ovarian, and breast cancers. Non-liposomal irinotecan is metabolised to an active metabolite SN-38 in the presence of hepatic or gastrointestinal carboxylesterases. The SN-38 metabolite is 100-1000-fold more cytotoxic than non-liposomal irinotecan which interacts specifically with the topoisomerase I enzyme, which results in lethal double-stranded DNA molecule breaks leading to activation of apoptosis and cell death. The key dose-limiting toxicities of non-liposomal irinotecan are gastrointestinal toxicity, particularly dual phase severe diarrhoea, and haematological toxicity, particularly leukopenia/neutropenia and anaemia.

ONIVYDE (also known as BAX2398, MM-398, or PEP02 or ONIVYDE® pegylated liposomal) is a proprietary liposomal formulation of irinotecan that has been developed using a novel intraliposomal stabilization technology. BAX2398 was invented at Hermes Biosciences, Inc. (Canada (CA), United States of America (USA)), and clinical development was commenced by PharmaEngine, Inc. (Taiwan). Since then, Merrimack Pharmaceuticals, Inc. (Cambridge, USA) acquired Hermes Biosciences, Inc. and had exclusive worldwide rights (except Taiwan rights) to develop and commercialize BAX2398 from PharmaEngine, Inc. Subsequently, Baxter International Inc. (IL, USA) acquired exclusive rights from Merrimack Pharmaceuticals, Inc., to develop and commercialize BAX2398 worldwide (except USA and Taiwan). Finally, Merrimack Pharmaceuticals, Inc. and Baxalta Inc. were acquired by Ipsen and Shire, respectively. Ipsen and Shire collaborated to develop BAX2398. Servier has acquired Shire's oncology business unit, including the rights to ONIVYDE outside of the USA and Taiwan and the MAH transfer activities from Shire/Baxalta to Servier has been approved in December 2018.

Ten clinical trials have been completed with ONIVYDE: three Phase I dose escalation/pharmacokinetic trials (PEP0201 and PEP0203 in advanced solid tumors, and

PIST-CRC-01 in metastatic colorectal cancer), one phase I study in breast cancer (MM-398-01-01-02), one Phase I/II trial for treatment of patients with cervical cancer (PEP0202), three Phase II trials for treatment of patients with gastric/gastroesophageal junction cancer (PEP0206) , pancreatic cancer (PEP0208) and metastatic pancreatic cancer in the Japanese population (331501), one Phase III pivotal trial for the treatment of patients with metastatic pancreatic cancer (NAPOLI-1) and one Phase II trial in first line pancreatic carcinoma (MM-398-07-02-03).
At the DLP of 22 April 2023, 4 clinical trials were ongoing: one Phase I dose escalation study in solid tumors (PEP0210) and one Phase I pharmacokinetic study in metastatic pancreatic cancer (D-FR-6001-015 or SIRACUSA), one Phase III study in Small Cell Lung Cancer (SCLC) (MM-398-01-03-04 or RESILIENT) and one Phase III study in first line pancreatic carcinoma (D-US-60010-001 or NAPOLI 3). Of note, recruitment for both Phase III studies was completed.

Previously, global health authorities have approved liposomal formulations containing the anticancer drugs doxorubicin and vincristine. The replacement of doxorubicin with its non-pegylated liposomal pharmaceutical analogue was well tolerated and effective in inducing remission in patients at high risk for cardiac toxicity or previously treated with anthracyclines (Rigacci et al. 2007). Further, pegylated liposomal doxorubicin hydrochloride (Caelyx) has also been shown to be effective. The first Marketing Authorisation Application (MAA) for ONIVYDE in the EU is for the indication of treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-FU and LV, in adult patients who have progressed following gemcitabine-based therapy. Marketing authorisation (centralized procedure) in this indication was granted on 14 October 2016.

Clinical Trial Exposure
The clinical trial exposure presented below includes data from the three Phase I dose escalation/pharmacokinetic trials (PEP0201, PEP0203, and PIST-CRC-01), three Phase I trials (MM-398-01-01-02, PEP0210 and D-FR-60010-015), one phase I/II trial for treatment of patients with cervical cancer (PEP0202), three Phase II trials for treatment of patients with gastric/gastroesophageal junction cancer (PEP0206) and pancreatic cancer (PEP0208 and 331501), two Phase III pivotal trials for the treatment of patients with metastatic pancreatic cancer (NAPOLI-1), and SCLC (RESILIENT), and two trials in first line pancreatic carcinoma: phase II trial (MM-398-07-02-03) and phase III (NAPOLI 3).

Please refer to the tables SIII.1., SIII.4 (2)., and SIII.5 (2). below for pooled clinical trial exposure data and to tables SIII.2., SIII.3., SIII.4 (1). and SIII.5 (1). for clinical trial exposure data by indication.

SIII.1. Duration of Exposure

Table SIII.1. Duration of Exposure (Overall)

Indication	Number of ONIVYDE Administrations	Summary
ALL ONIVYDE Exposed*,		1 274
	≥ 1 administration, n (%)	1 274 (100.0)
	≥ 2 administrations, n (%)	1 119 (87.8)
	≥ 3 administrations, n (%)	931 (73.1)
	≥ 4 administrations, n (%)	802 (63.0)

	≥ 5 administrations, n (%)	692 (54.3)
	Total Person Time[a]	11 629

[a] *Total Person Time is the cumulative number of administrations across all patients.*

**Data from studies PEP0201, PEP0202, PEP0203, PIST-CRC-01, PEP0206, PEP0208, PEP0210, 331501, MM-398-01-01-02, D-FR-60010-015, NAPOLI-1, RESILIENT, MM-398-07-02-03 and NAPOLI 3.*

SIII.2. Indication

Table SIII.2. Clinical Study Exposure by Indication

Indication	Number of ONIVYDE Administrations	Summary
ALL Pancreatic carcinoma*		838
	≥ 1 administration, n (%)	838 (100.0)
	≥ 2 administrations, n (%)	721 (86.0)
	≥ 3 administrations, n (%)	590 (70.4)
	≥ 4 administrations, n (%)	509 (60.7)
	≥ 5 administrations, n (%)	444 (53.0)
	Total Person Time[a]	8 009
Other indications **		436
	≥ 1 administration, n (%)	436 (100.0)
	≥ 2 administrations, n (%)	398 (91.3)
	≥ 3 administrations, n (%)	341 (78.2)
	≥ 4 administrations, n (%)	293 (67.2)
	≥ 5 administrations, n (%)	248 (56.9)
	Total Person Time[a]	3 620
Metastatic Pancreatic carcinoma, First line***		402
	≥ 1 administration, n (%)	402 (100.0)
	≥ 2 administrations, n (%)	363 (90.3)
	≥ 3 administrations, n (%)	330 (82.1)
	≥ 4 administrations, n (%)	310 (77.1)
	≥ 5 administrations, n (%)	283 (70.4)
	Total Person Time[a]	5041

[a] *Total Person Time is the cumulative number of administrations across all patients.*

**Data from studies PEP0208, 331501, D-FR-60010-015, NAPOLI-1, MM-398-07-02-03 and NAPOLI 3.*

***Data from studies PEP0201, PEP0202, PEP0203, PIST-CRC-01, PEP0206, PEP0210, MM-398-01-01-02, RESILIENT.*

**** Data from studies MM-398-07-02-03 and NAPOLI 3*

SIII.3. Age Group and Gender

Table SIII.3. Duration of Exposure by Age and Gender (By Indication)

		Persons		Person Time[a]	
Indication	**Age group**	**Male**	**Female**	**Male**	**Female**
ALL Pancreatic carcinoma*	<50	52	42	587	461
	50 - < 65	176	164	1 893	1 601
	65 - < 75	177	146	1 455	1 459
	75 and above	48	33	291	262
	Total	453	385	4 226	3 783
Other indications**	<50	35	44	361	295
	50 - < 65	116	96	892	848
	65 - < 75	78	45	654	387
	75 and above	15	7	93	90
	Total	244	192	2 000	1 620
Metastatic Pancreatic carcinoma, First line***	<50	26	24	392	320
	50 - < 65	82	80	1054	1021
	65 - < 75	85	74	938	995
	75 and above	17	14	148	173
	Total	210	192	2532	2509

[a] *Total Person Time is the cumulative number of administrations across all patients.*
**Data from studies PEP0208, 331501, D-FR-60010-015, NAPOLI-1, MM-398-07-02-03 and NAPOLI 3.*
***Data from studies PEP0201, PEP0202, PEP0203, PIST-CRC-01, PEP0206, PEP0210, MM-398-01-01-02, RESILIENT.*
**** Data from studies MM-398-07-02-03 and NAPOLI 3*

SIII.4. Ethnic Origin

Table SIII.4 (1). Duration of Exposure by Race and Ethnic Origin (By indication)

Indication	Ethnic or racial origin	Persons	Person Time[a]
ALL Pancreatic carcinoma*	Asian	179	1 376
	Black/African-American	20	247
	White	573	5 875
	American Indian or Alaska native	1	1
	Multiple	3	48
	Other	20	145
	Not reported	41	313
	Unknown	1	4
	Total	838	8 009

Other indications**	Asian	152	1206
	Black/African-American	5	70
	White	270	2 311
	American Indian or Alaska native	1	2
	Multiple	1	4
	Other	3	26
	Not reported	4	21
	Total	436	3 620
Metastatic Pancreatic carcinoma, First	Asian	21	368
	Black/African-American	13	195
	White	334	4088
	Multiple	3	48
	Other	7	96
	Not reported	24	246
	Total	402	5041

[a] *Total Person Time is the cumulative number of administrations across all patients.*

**Data from studies PEP0208, 331501, D-FR-60010-015, NAPOLI-1, MM-398-07-02-03 and NAPOLI 3.*

***Data from studies PEP0201, PEP0202, PEP0203, PIST-CRC-01, PEP0206, PEP0210, MM-398-01-01-02, RESILIENT.*

**** Data from studies MM-398-07-02-03 and NAPOLI 3*

Note: Race was not captured in Study PEP0201 and in Study PEP0203. These studies were carried out in Taiwan and all subjects in these studies were assumed to be Asian.

Table SIII.4 (2). Duration of Exposure by Race and Ethnic Origin (Overall)

Indication	Ethnic or racial origin	Persons	Person Time[a]
ALL ONIVYDE EXPOSED*	Asian	331	2 582
	Black/African-American	25	317
	White	843	8 186
	American Indian or Alaska native	2	3
	Native Hawaiian or other pacific islander	1	4
	Multiple	3	48
	Other	23	151
	Not reported	45	334
	Unknown	1	4
	Total	1 274	11 629

[a] *Total Person Time is the cumulative number of administrations across all patients.*

**Data from studies PEP0201, PEP0202, PEP0203, PIST-CRC-01, PEP0206, PEP0208, PEP0210, 331501, MM-398-01-01-02, D-FR-60010-015, NAPOLI-1, RESILIENT, MM-398-07-02-03 and NAPOLI 3.*

Note: Race was not captured in Study PEP0201 and in Study PEP0203. These studies were carried out in Taiwan and all subjects in these studies were assumed to be Asian.

SIII.5. Dose

Table SIII.5 (1). Duration of Exposure by Dose Regimen (By Indication)

Indication	ONIVYDE Regimen	Persons	Person Time[a]
ALL Pancreatic carcinoma*	ONIVYDE+OXALIPLATIN+5FU/LV, (Every 2 Weeks) Q2W	426	5 719
	ONIVYDE +5-FU/LV, Q2W	225	1 495
	ONIVYDE, Every 3 Weeks (Q3W)	187	795
	Total	838	8 009
Other indications**			
	ONIVYDE +5-FU/LV, Q3W	16	66
	ONIVYDE +CIS, Q3W	6	20
	ONIVYDE+TAS, Q2W	43	402
	ONIVYDE, Q2W	316	2 899
	ONIVYDE, Q3W	55	233
	Total	436	3 620
Metastatic Pancreatic carcinoma, First line***	ONIVYDE + OXALIPLATIN +5-FU/LV, Q2W	402	5041
	Total	402	5041

[a] *Total Person Time is the cumulative number of administrations across all patients.*
**Data from studies PEP0208, 331501, D-FR-60010-015, NAPOLI-1, MM-398-07-02-03 and NAPOLI 3.*
***Data from studies PEP0201, PEP0202, PEP0203, PIST-CRC-01, PEP0206, PEP0210, MM-398-01-01-02, RESILIENT.*
**** Data from studies MM-398-07-02-03 and NAPOLI 3*

Table SIII.5 (2). Duration of Exposure by Dose Regimen (Overall)

Indication	ONIVYDE Regimen	Persons	Person Time[a]
ALL ONIVYDE EXPOSED*	ONIVYDE + OXALIPLATIN +5-FU/LV, Q2W	426	5 719
	ONIVYDE +5-FU/LV, Q2W	225	1 495
	ONIVYDE +5-FU/LV, Q3W	16	66
	ONIVYDE +CIS, Q3W	6	20
	ONIVYDE+TAS, Q2W	43	402
	ONIVYDE, Q2W	316	2 899
	ONIVYDE, Q3W	242	1 028
	Total	1 274	11 629

[a] *Total Person Time is the cumulative number of administrations across all patients.*
**Data from studies PEP0201, PEP0202, PEP0203, PIST-CRC-01, PEP0206, PEP0208, PEP0210, 331501, MM-398-01-01-02, D-FR-60010-015, NAPOLI-1, RESILIENT, MM-398-07-02-03 and NAPOLI 3.*

Part II: Module SIV – Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Table SIV.1. Exclusion Criteria

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
Hypersensitivity to non-liposomal irinotecan or to any of the excipients in ONIVYDE	As with any drug, hypersensitivity reactions are possible. Severe hypersensitivity reactions may be life-threatening and, without immediate and effective care, may be fatal. Patients with hypersensitivity to the drug of any of the constituents should avoid use of the product.	No	Hypersensitivity is a known risk with ONIVYDE.
Breastfeeding Females	There is the potential for serious adverse reactions from ONIVYDE in nursing infants.	No	It is unknown whether ONIVYDE or its metabolites are excreted into human milk. Because of the potential for serious adverse reactions of ONIVYDE in breast-feeding infants, ONIVYDE is contraindicated in breast-feeding. Patients should not breast-feed until one month after the last dose.
Females of child-bearing potential were required to test negative for pregnancy at the time of enrolment based on a urine or serum pregnancy test.	The active substance, irinotecan, was found to be embryotoxic and teratogenic in animal studies.	No	Embryotoxicity/Teratogenicity is a known risk with ONIVYDE.
Patients with significant gastrointestinal disorder including hepatic disorders, GI bleeding, inflammation, bowel occlusion, or diarrhoea greater than Grade 1.	Inclusion of patients with these conditions would have confounded the frequency estimate for these disorders as Treatment Emergent Adverse Events (TEAEs) in the clinical trial and increased the risk of severe/serious of diarrhoea.	No	Diarrhoea is a known risk with ONIVYDE.
Severe arterial thromboembolic events (myocardial infarction, unstable angina pectoris, stroke) less than 6 months before inclusion.	Patients with thrombotic disease were excluded to allow for the determination of the occurrence of thromboembolic events in patients not at increased risk. Coagulation disorders can be associated with a higher risk of thrombus or clot formation leading to stroke,	No	Thromboembolic events are known risks with ONIVYDE.

Table SIV.1. Exclusion Criteria

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
	myocardial infarction, pulmonary embolism, and possibly death.		
History of Interstitial lung disease (ILD), history of slowly progressive dyspnoea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies.	A medical history of lung disease is a risk factor for developing ILD-like events and put the patients at increased risk in clinical trials.	No	ILD is a known important potential risk with ONIVYDE.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or by those caused by prolonged and cumulative exposure.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table SIV.3. Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment	In clinical studies of irinotecan, the active ingredient of ONIVYDE, 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. The use of ONIVYDE 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. 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 is given in combination with other hepatotoxic medicinal products, especially in patients with pre-existing hepatic impairment. Dose adjustment may be needed for patients with Grade 3 or 4 hepatic toxicities.
• Patients with renal impairment	In the clinical development program for ONIVYDE, adequate renal function (defined as a serum creatinine ≤ 1.5 x ULN) was required for inclusion. No dose adjustment is recommended in patients with mild to moderate renal impairment.

Table SIV.3. Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of special population	Exposure
• Elderly patients	ONIVYDE is not recommended for use in patients with severe renal impairment (CLcr < 30 ml/min). Of the 412 patients treated across the clinical program with ONIVYDE, 170 (41%) patients studied were ≥ 65 years. Overall, no major clinical differences in safety or efficacy were reported between patients ≥ 65 years and patients < 65 years, although a higher frequency of discontinuation (14.8% vs 7.9%) was noted in the former group treated with ONIVYDE+5-FU/LV in the NAPOLI-1 study 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+5-FU/LV in the pancreatic adenocarcinoma study. In NAPOLI 3 study, 50.1% of participants were over 65 years of age. Safety results from NAPOLI 3 showed no difference in TEAE profile due to age. No dose modifications are proposed for patients ≥ 65 years of age.
Population with relevant different ethnic origin	Clinical studies with ONIVYDE included patients that were Caucasian, Black/African American, Asian, and American Indian/Alaska native patients. Neutropenia is more frequent and severe in Asians compared to Caucasians, with higher frequency of neutropenic fever/sepsis and sepsis/bacteraemia reported in Asians compared to Caucasians. Diarrhoea is more frequent and severe in Caucasians compared to Asians with higher frequency of hypokalaemia, hypomagnesaemia and dehydration as a consequence. The differences in neutropenia and diarrhoea may be partially explained by the exposure differences observed between Asians and Caucasians of non-liposomal irinotecan and SN-38 following ONIVYDE administration. Additional notable clinically relevant differences in the frequency of other Adverse Events (AEs) include a higher rate of nausea, vomiting, decreased appetite and alopecia were reported for Asians compared to Caucasians in ONIVYDE containing arms and fatigue was reported with higher frequency in the Caucasians compared to Asians.
Patients homozygous for the *UGT1A1*28* or UGT1A1*6 allele	Clinical studies with ONIVYDE included patients homozygous for the *UGT1A1*28* or UGT1A1*6 allele. In NAPOLI 1 study, patients who screened homozygous for the UGT1A1*28 or UGT1A1*6 alleles or had both alleles received an adjusted reduced starting dose of ONIVYDE [increased as tolerated] as defined in the study protocol. In NAPOLI 3 study, the starting dose of ONIVYDE in patients known to be homozygous for UGT1A1*28 allele was unchanged and remained at 50 mg/m^2. Individuals who are homozygous for the *UGT1A1*28* allele are at an increased risk for neutropenia from irinotecan Hydrochloride (HCL)[i]

Part II: Module SV – Post-Authorization Experience

SV.1. Post-Authorization Exposure

SV.1.1 Method Used to Calculate Exposure

The method used to estimate patient exposure for liposomal irinotecan is based on the following three parameters:

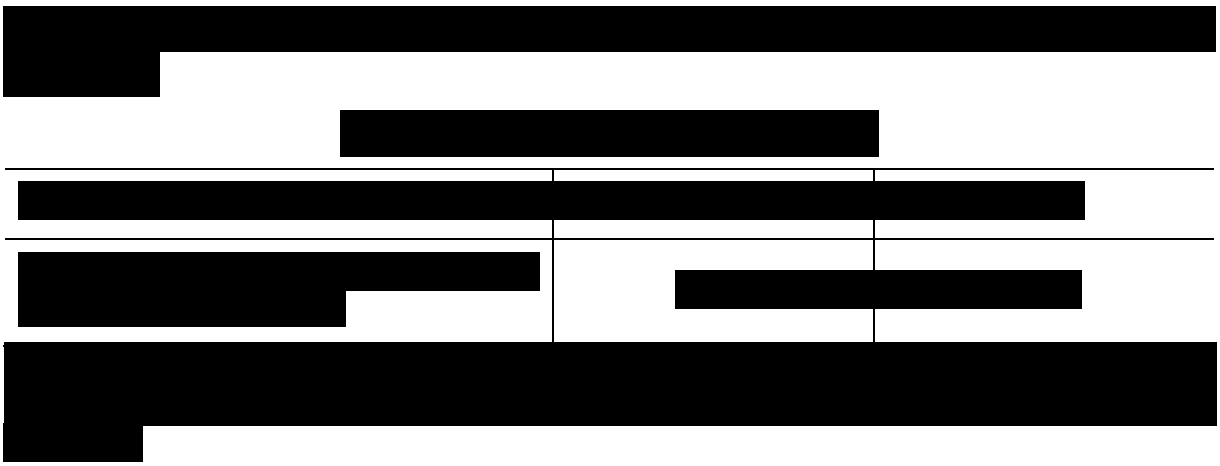
a) Total number of vials distributed/sold;
b) Average number of vials used per patient per cycle;
c) Estimated average cycles per patient.

Variables "a" and "c" are changing numbers based on sales and current utilisation data whereas variable "b" is a relative constant based on dosing instructions. The relationships of all three parameters are provided in the equation below.

$$\text{Estimated no of Patients} = \frac{\text{Total number of vials distributed/sold}}{\text{Avg vials per patient per cycle [x]estimated avg cycles per patient}}$$

*Average number of vials per patient per cycle = 2.9 and Estimated average cycles per patient 4.37

SV.1.2 Exposure



Part II: Module SVI – Additional EU Requirements for the Safety Specification

SVI.1. Potential for Misuse for Illegal Purposes

As an intravenous oncology agent administered solely within a secondary or tertiary hospital setting, there is no potential for misuse of ONIVYDE for illegal purposes.

Part II: Module SVII – Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

The following safety concerns have been removed in Risk Management Plan (RMP) version 3.0 (dated 28 November 2019): Diarrhoea, Leukopenia/Neutropenia, Anaemia, Acute infusion reactions, previously classified as important identified risks, Embryotoxicity/teratogenicity, Hypersensitivity reactions, Interstitial lung disease, Medication error related to drug/dose confusion with non-liposomal irinotecan, previously classified as important potential risks, Use in patients with hepatic impairment and Use in patients with renal impairment, previously classified as missing information, due to a regulatory request (Procedure no.: EMEA/H/C/PSUSA/00010534/201810).

In RMP version 4.0 (dated 27 May 2022), Medication error related to dosing error due to the change in the way the strength is expressed, previously classified as important potential risk, is removed from the list of safety concerns considering that this risk does not impact the risk-benefit profile. Indeed, the harmonisation of the strength designation has now been implemented worldwide. Only the new expression of strength is now available on the market and cumulatively only one non serious case of medication error with no associated Adverse Drug Reaction (ADR) was reported. This review was performed following PRAC request (procedure EMA/H/C/PSUSA/00010534/202010).

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table SVII.3.1. Important Identified Risk: Thromboembolic events

Potential mechanisms	The mechanism behind a true (i.e., not due to extraneous factors) drug-related thromboembolism is poorly understood. Some oncology agents can induce vascular damage, either directly or indirectly, thereby promoting local activation of the coagulation process.
Evidence source(s) and strength of evidence	Thromboembolic events have been reported in clinical trials and medical literature.
Characterisation of the risk	In the NAPOLI-1 study, thromboembolic events were reported in up to 6% treated with ONIVYDE in combination with 5-FU and LV and up to 14.3% of patients treated with ONIVYDE alone. In NAPOLI-3 study, thromboembolic events were reported in 21.9% of patients treated with ONIVYDE in combination with oxaliplatin and 5-FU/LV. In clinical studies with ONIVYDE, deep vein thrombosis, pulmonary embolism, and embolism were considered common adverse reactions (≥1/100 to <1/10).
Risk factors and risk groups	Risk of thromboembolism in cancer patients depends on the tumour type, stage of the disease, surgical intervention, presence of an indwelling central venous catheter, age, and a previous history of thromboembolism. There are no risk factors specific to non-liposomal irinotecan. Risk of venous thromboembolism was found to be highest among patients with cancers of the pancreas, brain, and lung. However, this can vary widely by cancer type and time since diagnosis (Timp et al. 2013). Altered liver function may contribute to impaired coagulation or coagulation complications. As such, patients with liver disease maybe at greater risk for thromboembolic events.
Preventability	Routine prophylaxis with an anticoagulant in patients undergoing adjuvant chemotherapy or palliative chemotherapy is not usually recommended. Use of an anticoagulant is determined by individual patient risk.

Table SVII.3.1. Important Identified Risk: Thromboembolic events

Impact on the risk-benefit balance of the product	Thromboembolic events will continue to be monitored through routine pharmacovigilance and routine risk minimisation measures. The benefit-risk profile of ONIVYDE remains positive.
Public health impact	Ischaemic cerebral infarction may result in long-term patient care and rehabilitation, ranging from days to months.

SVII.3.2 Presentation of the Missing Information

Not applicable

Part II: Module SVIII – Summary of the Safety Concerns

Table SVIII.1. Summary of Safety Concerns

Important identified risks	Thromboembolic events
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Currently there are no routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

III.2 Additional Pharmacovigilance Activities

There are no additional pharmacovigilance activities.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

Part IV: Plans for Post-Authorisation Efficacy Studies

None.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1 Routine Risk Minimisation Measures

Table Part V.1. Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Thromboembolic Events	**Routine risk communication:** SmPC Section 4.2 – Posology and method of administration SmPC Section 4.8 – Undesirable effects PL Section 4 – Possible side effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 **–** Tables 1, 2 and 3, Recommended dose modifications for ONIVYDE. SmPC Section 4.4: 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. PL Section 4 – Patients should notify their doctor immediately if they have any blood clots **Other routine risk minimisation measures beyond the Product Information** None.

V.2 Additional Risk Minimisation Measures

None.

V.2.1 Removal of Additional Risk Minimisation Activities

Not Applicable.

V.3 Summary of Pharmacovigilance Activities and Risk Minimisation Measures

Table Part V.3. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation activities	Pharmacovigilance activities
Thromboembolic events	**Routine risk minimisation measures:** SmPC Section 4.2 **–** Tables 1, 2 and 3 Recommended dose modifications for ONIVYDE. SmPC Section 4.4: 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. SmPC Section 4.8 PL Section 4 – Patients should notify their doctor immediately if they have any blood clots. **Additional risk minimisation measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** No additional pharmacovigilance activities.

Table Part V.3. Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation activities	Pharmacovigilance activities
	No risk minimisation activities.	

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for ONIVYDE (liposomal irinotecan)

This is a summary of the RMP for ONIVYDE. The RMP details important risks of ONIVYDE, how these risks can be minimised, and how more information will be obtained about ONIVYDE's risks and uncertainties (missing information).

ONIVYDE's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ONIVYDE should be used.

This summary of the RMP for ONIVYDE should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of ONIVYDE's RMP.

I. The medicine and what it is used for

ONIVYDE is authorised in combination with oxaliplatin, 5-fluorouracil (5-FU) and leucovorin (LV) in first line treatment of adult patients with metastatic adenocarcinoma of the pancreas and in combination with 5-fluorouracil (5-FU) and leucovorin (LV), in adult patients who have progressed following gemcitabine-based therapy (see SmPC for the full indication). It contains irinotecan encapsulated in a lipid bilayer vesicle or liposome as the active substance and it is given intravenously.

Further information about the evaluation of ONIVYDE's benefits can be found in ONIVYDE's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of ONIVYDE, together with measures to minimise such risks and the proposed studies for learning more about ONIVYDE's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient For Example (e.g.) (with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of ONIVYDE is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of ONIVYDE are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ONIVYDE. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table II.A List of important risks and missing information

Important identified risks	Thromboembolic events
Important potential risks	None
Missing information	None

II.B Summary of important risks

Table II.B Summary of important risks

Important Identified Risk: Thromboembolic Events	
Evidence for linking the risk to the medicine	Thromboembolic events have been reported in clinical trials and medical literature.
Risk factors and risk groups	Risk of thromboembolism in cancer patients depends on the tumour type, stage of the disease, surgical intervention, presence of an indwelling central venous catheter, age, and a previous history of thromboembolism. There are no risk factors specific to non-liposomal irinotecan. Risk of venous thromboembolism was found to be highest among patients with cancers of the pancreas, brain, and lung. However, this can vary widely by cancer type and time since diagnosis (Timp et al. 2013). Altered liver function may contribute to impaired coagulation or coagulation complications. As such, patients with liver disease maybe at greater risk for thromboembolic events.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 – Tables 1, 2 and 3 Recommended dose modifications for ONIVYDE. SmPC Section 4.4: 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. SmPC Section 4.8 PL Section 4 – Patients should notify their doctor immediately if they have any blood clots. **Additional risk minimisation measures:** No risk minimisation measures.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of ONIVYDE.

II.C.2 Other studies in the post-authorisation development plan

There are no studies required for ONIVYDE.

Part VII Annexes

Annex 1 - Eudravigilance Interface

Annex 2 - Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Annex 4 - Specific adverse drug reaction follow-up forms

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Annex 6 - Details of proposed additional risk minimisation activities

Annex 7 - Other supporting data (including referenced material)

Annex 8 - Summary of changes to the risk management plan over time

Annex 4 - Specific adverse drug reaction follow-up forms

There are no specific adverse drug reaction follow-up forms for ONIVYDE.

Annex 6 - Details of proposed additional risk minimisation activities

Not applicable.