1. NAME OF THE MEDICINAL PRODUCT

ONIVYDE 5 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 10 ml vial of concentrate contains the equivalent of 50 mg irinotecan hydrochloride trihydrate (as irinotecan sucrosofate salt in a pegylated liposomal formulation) which corresponds to 43 mg irinotecan.

One ml of concentrate contains the equivalent of 5 mg irinotecan hydrochloride trihydrate (as irinotecan sucrosofate salt in a pegylated liposomal formulation) which corresponds to 4.3 mg irinotecan.

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 solution 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

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.

4.2 Posology and method of administration

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

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

Posology

ONIVYDE, leucovorin and 5-fluorouracil should be administered sequentially. The recommended dose and regimen of ONIVYDE is 80 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. ONIVYDE should not be administered as a single agent.

A reduced starting dose of ONIVYDE (liposomal irinotecan) of 60 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 80 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.

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

For patients who start treatment with 60 mg/m^2 ONIVYDE and do not dose escalate to 80 mg/m^2, the recommended first dose reduction is to 50 mg/m^2 and the second dose reduction is to 40 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 60 mg/m^2) may have the dose of ONIVYDE increased to a total dose of 80 mg/m^2 in subsequent cycles based on individual patient tolerance.

Table 1: Recommended dose modifications for ONIVYDE+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/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 ≥ 1500/mm^3	
Grade 3 or Grade 4 (< 1000/mm^3) **or Neutropenic fever**	***First occurrence***	Reduce ONIVYDE dose to 60 mg/m^2 Reduce 5-FU dose by 25% (1800 mg/m^2)
	Second occurrence	Reduce ONIVYDE dose to 50 mg/m^2 Reduce 5-FU dose by an additional 25% (1350 mg/m^2)
	Third occurrence	Discontinue treatment
Thrombocytopenia **Leukopenia**	A new cycle of therapy should not begin until the platelet count is ≥ 100,000/mm^3 Dose modifications for leukopenia and thrombocytopenia are based on NCI CTCAE toxicity grading and are the same as recommended for neutropenia above.	
Nonhaematological toxicities[2]		
Diarrhoea	A new cycle of therapy should not begin until diarrhoea resolves to ≤ Grade 1 (2-3 stools/day more than pre-treatment frequency).	
Grade 2	A new cycle of therapy should not begin until diarrhoea resolves to ≤ Grade 1 (2-3 stools/day more than pre-treatment frequency).	

Toxicity grade (value) by NCI CTCAE v 4.0[1]	**ONIVYDE/5-FU adjustment (for patients not homozygous for UGT1A1*28)**	
Grade 3 or 4	***First occurrence***	Reduce ONIVYDE dose to 60 mg/m^2 Reduce 5-FU dose by 25% (1800 mg/m^2)
	Second occurrence	Reduce ONIVYDE dose to 50 mg/m^2 Reduce 5-FU dose by an additional 25% (1350 mg/m^2)
	Third occurrence	Discontinue treatment
Nausea/vomiting	A new cycle of therapy should not begin until nausea/vomiting resolves to ≤ Grade 1 or baseline	
Grade 3 or 4 *(despite antiemetic therapy)*	***First occurrence***	Optimise antiemetic therapy Reduce ONIVYDE dose to 60 mg/m^2
	Second occurrence	Optimise antiemetic therapy Reduce ONIVYDE dose to 50 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 dose to 60 mg/m^2 Reduce 5-FU dose by 25% (1800 mg/m^2)
	Second occurrence	Reduce ONIVYDE dose to 50 mg/m^2 Reduce 5-FU dose by an additional 25% (1350 mg/m^2)
	Third occurrence	Discontinue treatment
Anaphylactic reaction	***First occurrence***	Discontinue treatment

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

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

Table 2: Recommended dose modifications for ONIVYDE +5-FU/LV for Grade 3-4 toxicities in patients homozygous for UGT1A1*28

Toxicity grade (value) by NCI CTCAE v 4.0[1]	**ONIVYDE/5-FU adjustment (for patients homozygous for UGT1A1*28 without previous increase to 80 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 dose to 50 mg/m^2 5-FU dose modification as in Table 1
	Second occurrence	Reduce ONIVYDE dose to 40 mg/m^2 5-FU dose modification as in Table 1
	Third occurrence	Discontinue treatment

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

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

Special populations

Hepatic impairment
No dedicated hepatic impairment study has been conducted with ONIVYDE. 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 (see section 4.4).

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

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

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

Method of administration

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

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

4.3 Contraindications

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 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 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 has been demonstrated.

Myelosuppression/neutropenia

Complete blood cell count monitoring is recommended during ONIVYDE treatment. Patients should be aware of the risk of neutropenia and the significance of fever. The median time to nadir for ≥ Grade 3 neutropenia is 23 (range 8-104) days post first dose of treatment with ONIVYDE. 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. ONIVYDE should be withheld if neutropenic fever occurs or the absolute neutrophil count drops below 1500/mm^3. Sepsis with neutropenic fever and consequent septic shock with fatal outcome has been observed in patients with metastatic pancreatic adenocarcinoma treated with ONIVYDE.
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.
History of prior abdominal radiation increases the risk of severe neutropenia and febrile neutropenia following ONIVYDE treatment. Close monitoring of blood counts is recommended, and the use of myeloid growth factors should be considered for patients with a history of abdominal radiation. Caution should be exercised in patients receiving concurrent administration of ONIVYDE with irradiation.

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.

Compared to Caucasian patients, Asian patients have an increased risk of severe and febrile neutropenia following treatment with ONIVYDE+5-FU/LV (see sections 4.8 and 5.2).

Immunosuppressive effects and vaccines

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic medicinal products including ONIVYDE 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 should not be administered with strong CYP3A4-enzyme inducers such as anticonvulsants (phenytoin, phenobarbital or carbamazepine), rifampin, 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 non-enzyme inducing therapies at least 2 weeks prior to initiation of ONIVYDE therapy (see section 4.5).

Interactions with strong CYP3A4 inhibitors or strong UGT1A1 inhibitors

ONIVYDE should not be administered with strong CYP3A4-enzyme 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 therapy.
ONIVYDE should not be administered with strong UGT1A inhibitors (e.g. atazanavir, gemfibrozil, indinavir) unless there are no therapeutic alternatives.

Diarrhoea

Diarrhoea can occur early (onset in ≤ 24 hours after starting ONIVYDE) or late (> 24 hours) (see section 4.8).
In patients experiencing early diarrhea, therapeutic and prophylactic 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. Loperamide should be given until patient is without diarrhoea for at least 12 hours.
If diarrhoea persists while 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.
ONIVYDE treatment should be delayed until diarrhoea resolves to ≤ Grade 1 (2-3 stools/day more than pre-treatment frequency). ONIVYDE must not be administered to patients with bowel obstruction, and chronic inflammatory bowel disease, until it is resolved.
Following Grade 3 or 4 diarrhoea, the subsequent dose of ONIVYDE 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.

Acute infusion and related reactions

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

Prior Whipple procedure

Patients with a history of a Whipple procedure have a higher risk of serious infections following ONIVYDE in combination with 5-FU and leucovorin (see section 4.8). Patients should be monitored for signs of infections.

Vascular disorders

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

Pulmonary toxicity

Interstitial Lung Disease (ILD)-like events leading to fatalities have occurred in patients receiving non-liposomal irinotecan. No cases of ILD-like events have been reported with ONIVYDE therapy in clinical studies. Risk factors include pre-existing lung disease, use of pneumotoxic medicinal products, colony stimulating factors or having previously received radiation therapy. Patients with risk factors should be closely monitored for respiratory symptoms before and during ONIVYDE therapy. 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 treatment, pending diagnostic evaluation. ONIVYDE should be discontinued in patients with a confirmed diagnosis of ILD.

Hepatic impairment

Patients with hyperbilirubinaemia had higher concentrations for total SN-38 (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 is given in combination with other hepatotoxic medicinal products, especially in patients with pre-existing hepatic impairment.

Renal impairment

The use of ONIVYDE in patients with significant renal impairment has not been established (see section 5.2).

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

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

Excipients

Each ml of ONIVYDE contains 0.144 mmol (3.31 mg) sodium. This needs to be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Information about drug interactions with ONIVYDE is referenced from the published scientific literature for nonliposomal irinotecan.

Interaction affecting the use of ONIVYDE

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 with inducers of CYP3A4 may reduce systemic exposure of ONIVYDE.

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 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. Based on the drug interaction of non-liposomal irinotecan and ketoconazole, co-administration of ONIVYDE with other inhibitors of UGT1A1 (e.g. atazanavir, gemfibrozil, indinavir) may also increase systemic exposure of ONIVYDE.

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

No interaction of ONIVYDE (liposomal irinotecan) 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 treatment and 1 month thereafter. Males should use condoms during ONIVYDE treatment and 4 months thereafter.

Pregnancy

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

Breast-feeding

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 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 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).

4.7 Effects on ability to drive and use machines

ONIVYDE 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

The following adverse reactions, considered to be possibly or probably related to the administration of ONIVYDE, were reported in 264 patients with metastatic adenocarcinoma of the pancreas, 147 of whom received ONIVYDE monotherapy (120 mg/m^2) and 117 received ONIVYDE (80 mg/m^2) in combination with 5-FU/LV.
The most common adverse reactions (incidence ≥ 20%) of ONIVYDE+5FU/LV were: diarrhoea, nausea, vomiting, decreased appetite, neutropenia, fatigue, asthenia, anaemia, stomatitis and pyrexia.
The most common serious adverse reactions (≥ 2%) of ONIVYDE therapy were diarrhoea, vomiting, febrile neutropenia, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.
The rates of adverse reactions leading to permanent treatment discontinuation were 11% for the ONIVYDE+5-FU/LV arm and 12% for the monotherapy arm.
The most frequently reported adverse reactions leading to discontinuation were infection and diarrhoea for ONIVYDE+5-FU/LV arm, and vomiting and diarrhoea for the monotherapy arm.

Tabulated list of adverse reactions

The adverse reactions that may occur during treatment with ONIVYDE are summarised below and are presented by system organ class and frequency category (Table 3). Within each system organ class and frequency category, adverse reactions are presented in order of decreasing seriousness. Frequencies categories used for adverse reactions are: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100) and rare (≥ 1/10,000 to < 1/1,000)**.

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

MedDRA* system organ class	**Adverse reaction frequency****
Infections and infestations	*Common:* Septic shock, Sepsis, Pneumonia, Febrile neutropenia, Gastroenteritis, Oral candidiasis *Uncommon:* Biliary sepsis
Blood and lymphatic system disorders	*Very common:* Neutropenia, Leukopenia, Anaemia, Thrombocytopenia *Common:* Lymphopenia
Immune system disorders	*Uncommon: Hypersensitivity*
Metabolism and nutrition disorders	*Very common:* Hypokalaemia, Hypomagnesaemia, Dehydration, Decreased appetite *Common:* Hypoglycaemia, Hyponatraemia, Hypophosphataemia
Psychiatric disorders	*Common:* Insomnia
Nervous system disorders	*Very common:* Dizziness *Common:* Cholinergic syndrome, Dysgeusia
Cardiac disorders	*Common:* Hypotension
Vascular disorders	*Common*: Pulmonary embolism, Embolism, Deep vein thrombosis *Uncommon:* Thrombosis
Respiratory, thoracic and mediastinal disorders	*Common*: Dyspnoea, Dysphonia *Uncommon:* Hypoxia
Gastrointestinal disorders	*Very common:* Diarrhoea, Vomiting, Nausea, Abdominal pain, Stomatitis *Common:* Colitis, Haemorrhoids *Uncommon:* Oesophagitis, Proctitis
Hepatobiliary disorders	*Common:* Hypoalbuminaemia
Skin and subcutaneous tissue disorders	*Very common:* Alopecia *Uncommon:* Rash maculo-papular, Nail discolouration
Renal and urinary disorders	*Common:* Acute renal failure
General disorders and administration site conditions	*Very common:* Pyrexia, Peripheral oedema, Mucosal inflammation, Fatigue, Asthenia *Common:* Infusion related reaction, Oedema

MedDRA* system organ class	Adverse reaction frequency**
Investigations	*Very common*: Weight decrease *Common*: Increased bilirubin, Increased alanine aminotransferase, Increased aspartate aminotransferase, Increased international normalized ratio

* MedDRA version 14.1

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

Description of selected adverse reactions

The following adverse reactions were observed in the NAPOLI-1 clinical study:

Myelosuppression

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

Neutropenia/leukopenia

Neutropenia/leukopenia was the most notable important haematological toxicity. Grade 3 or higher neutropenia occurred more frequently in patients treated with ONIVYDE+5-FU/LV (27.4%) compared to patients treated with 5-FU/LV (1.5%). Neutropenic fever/sepsis appeared more frequently in the ONIVYDE+5-FU/LV combination arm [in 4 patients (3.4%)] compared to 5-FU/LV control arm [in 1 patient (0.7%)].

Thrombocytopenia

Grade 3 or higher thrombocytopenia occurred in 2.6% of patients treated with ONIVYDE+5-FU/LV and 0% in patients treated with 5-FU/LV.

Anaemia

Grade 3 or higher anaemia occurred in 10.3% of patients treated with ONIVYDE+5-FU/LV and in 6.7% of patients treated with 5-FU/LV.

Acute renal failure

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

Diarrhoea and related adverse reactions

Diarrhoea is a very common adverse reaction leading to colitis, ileus, gastroenteritis, fatigue, dehydration, weight loss, renal toxicities, hyponatraemia, and hypokalaemia. Renal impairment and acute renal failure have been identified, usually in patients who became volume depleted from severe vomiting and/or diarrhoea. In the clinical study Grade 3 or Grade 4 diarrhoea occurred in 15 out of 117 patients (12.8%) receiving ONIVYDE+5-FU/LV. For patients experiencing late diarrhoea, the median time to late diarrhoea onset was 8 days from the previous dose of ONIVYDE. Early onset diarrhoea, typically appearing ≤24 hours after dose administration, can occur 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. In the clinical study, early diarrhoea onset occurred in 35 patients (29.9%) and cholinergic events occurred in 4 patients (3.4%) receiving ONIVYDE+5-FU/LV.

Withhold ONIVYDE for Grade 2-4 diarrhoea and initiate treatment for diarrhoea. Following recovery to Grade 1 diarrhoea, resume ONIVYDE at a reduced dose (see section 4.2).

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

Other special populations

Elderly
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.

Asian population
Compared to Caucasians, Asian patients were observed with a lower incidence of diarrhoea [14 (19.2%) out of 73 Caucasians had a ≥ Grade 3 diarrhoea, and 1 out of 33 (3.3%) Asians had a ≥ Grade 3 diarrhoea], but a higher incidence and higher severity of neutropenia. In patients receiving ONIVYDE+5-FU/LV, the incidence of ≥ Grade 3 neutropenia was higher among Asian patients [18 of 33 (55%)] compared to White patients [13 of 73 (18%)]. Neutropenic fever/neutropenic sepsis was reported in 6% of Asian patients compared to 1% of White patients. This is consistent with the population pharmacokinetic analysis that showed a lower exposure to irinotecan and a higher exposure to its active metabolite SN-38 in Asians than in Caucasians.

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

Patients with UGT1A1 allele
Individuals who are 7/7 homozygous for the UGT1A1*28 allele are at increased risk for neutropenia from non-liposomal irinotecan. In the clinical study evaluating ONIVYDE+5-FU/LV, 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 of 80 mg/m^2 [30 of 110 (27.3%)] (see section 5.1).

Underweight patients (body mass index < 18.5 kg/m^2)
In the clinical study evaluating ONIVYDE+5-FU/LV, 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).

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

The active substance in ONIVYDE 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 metabolized by carboxylesterase to SN-38. SN-38 is approximately 1000 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 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

The safety and efficacy of ONIVYDE were investigated in a multinational, randomized, open label, controlled clinical trial (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 trial was designed to assess the clinical efficacy and safety of ONIVYDE monotherapy or ONIVYDE+5-FU/LV compared to an active control arm of 5-FU/LV.

Patients randomized to ONIVYDE+5-FU/LV received ONIVYDE at 80 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 (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 monotherapy received 120 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) ≥ 70, normal bilirubin level, transaminase levels ≤ 2.5 times the ULN or ≤ 5 times the ULN for patients with liver metastases and albumin ≥ 3.0 g/dl.

A total of 417 patients were randomised to the ONIVYDE+5-FU/LV arm (N=117), ONIVYDE monotherapy arm (N=151) and 5-FU/LV arm (N=149). Patient demographic and entry disease characteristics were well balanced between trial 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 White 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 4. Overall survival is illustrated in Figure 1.

Table 4: Efficacy results from NAPOLI-1 clinical study

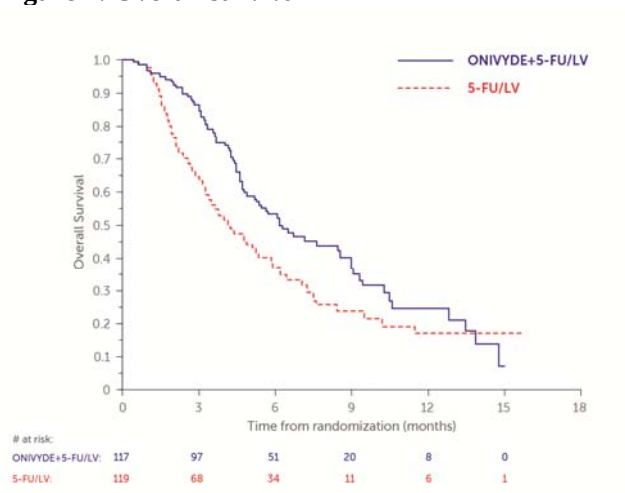
	ONIVYDE+5-FU/LV (N= 117)	**5-FU/LV (N= 119)**
Overall Survival[1]		
Number of deaths, n (%)	**75 (64)**	**80 (67)**
Median OS (months)	6.1	4.2
(95% CI)	(4.8, 8.9)	(3.3, 5.3)
Hazard Ratio (95% CI)[3]	0.67 (0.49-0.92)	
p-value[4]	0.0122	
Progression-Free Survival[1,2]		
Death or progression, n (%)	83 (71)	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	

	ONIVYDE+5-FU/LV (N= 117)	**5-FU/LV (N= 119)**
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 1: Overall survival



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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with ONIVYDE in all subsets of the paediatric population in treatment of adenocarcinoma of the pancreas (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, as a single agent or as part of combination chemotherapy, at doses between 60 and 180 mg/m2. The pharmacokinetic parameters of total irinotecan and SN-38 analytes, following the administration of ONIVYDE 80 mg/m2 are presented in Table 5.

Table 5: Summary of mean (±standard deviation) total irinotecan and total SN-38

Analyte	**PK parameters**	**Unit**	**ONIVYDE geomean (95% CI)[a] 80 mg/m^2(n=353)[b]**	**Non-liposomal irinotecan mean (SD) 125 mg/m^2 (n=99)[c]**
Total irinotecan	AUC	h ng/ml	919228 (845653-999204)	10529 (3786)
	C_{max}	ng/ml	28353 (27761-28958)	1492 (452)
	Clearance (CL)	l/h/m2	0.087 (0.080-0.094)	13.0 (5.6)
	Volume (V)	l/m2	2.6 (2.6-2.7)	138 (60.9)
	$t_{1/2\ effective}$	h	20.8 (19.4-22.3)	6.07 (1.19)
Total SN-38	AUC	h ng/ml	341 (326-358)	267 (115)
	C_{max}	ng/ml	3.0 (2.9-3.1)	27.8 (11.6)
	$t_{1/2\ effective}$	h	40.9 (39.8-42.0)	11.7 (4.29)

SD= standard deviation
AUC= area under the plasma concentration curve (extrapolated to infinity for ONIVYDE and AUC24h for non-liposomal irinotecan)
C_{max}= maximum plasma concentration
$t_{1/2\ effective}$= effective half-lives
[a]Values are estimated from population PK analysis
[b]N=353 refers to all the subjects included in the population PK analysis
[c]Values are obtained from published data [Schaaf LJ et al. *Clin Cancer Res*. 2006 Jun 15;12:3782-91]

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 80 mg/m^2 was 2.6 l/m^2, which suggests that ONIVYDE is largely confined to vascular fluid.
The plasma protein binding of ONIVYDE is negligible (< 0.44% of total irinotecan in ONIVYDE). The plasma protein binding of non-liposomal irinotecan is moderate (30% to 68%), and SN-38 is highly bound to human plasma proteins (approximately 95%).

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 in patients with ONIVYDE using the results of a subset with UGT1A1*28 genotypic testing, in which the analysis adjusted for the lower dose administered to patients homozygous for the UGT1A1*28 allele, patients homozygous (N=14) and non-homozygous (N=244) for this allele had total SN-38 average steady-state concentrations of 1.06 and 0.95 ng/ml, respectively.

Elimination

The disposition of ONIVYDE and non-liposomal irinotecan has not been fully elucidated in humans.
The urinary excretion of non-liposomal irinotecan is 11% to 20%; SN-38 <1%; and SN-38 glucuronide is 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of irinotecan in two patients ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2).

Renal impairment

No dedicated pharmacokinetic study has been conducted in patients with renal impairment. In a population pharmacokinetic analysis, mild-to-moderate renal impairment had no effect on the exposure of total SN-38 after adjusting for BSA. The analysis included 68 patients with moderate (CLcr 30-59 ml/min), 147 patients with mild (CLcr 60-89 ml/min) renal impairment, and 135 patients with normal renal function (CLcr > 90 ml/min). There was insufficient data in patients with severe renal impairment (CLcr < 30 ml/min) to assess its effect on pharmacokinetics (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, patients with baseline total bilirubin concentrations of 1-2 mg/dl (n=19) had average steady state concentrations for total SN-38 that were increased by 37% (0.98 [95%CI: 0.94-1.02] and 1.29 [95%CI: 1.11-1.5] ng/ml, respectively) compared to patients with baseline bilirubin concentrations of < 1 mg/dl (n=329); however, there was no effect of elevated ALT/AST concentrations on total SN-38 concentrations. No data are available in patients with total bilirubin more than 2 times the ULN.

Other special populations

Age and gender
The population pharmacokinetic analysis in patients aged 28 to 87 years, of whom 11% were ≥75 years suggests that age had no clinically meaningful effect on the exposure to irinotecan and SN-38.
The population pharmacokinetic analysis in 196 male and 157 female patients suggests that gender had no clinically meaningful effect on the exposure to irinotecan and SN-38 after adjusting for body surface area (BSA).

Ethnicity
The population pharmacokinetic analysis suggest that Asians have 56% lower total irinotecan average steady state concentration (3.93 [95%CI: 3.68-4.2] and 1.74 [95%CI: 1.58-1.93] mg/l, respectively)

and 8% higher total SN-38 average steady state concentration (0.97 [95%CI: 0.92-1.03] and 1.05 [95%CI: 0.98-1.11] ng/ml, respectively) than Caucasians.

Pharmacokinetic/pharmacodynamic relationship

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

In the clinical trial demonstrating effectiveness of ONIVYDE, higher plasma exposures of total irinotecan and SN-38 for patients in the ONIVYDE+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 hematologic system. The severity of effects was dose-related and reversible. The no-observed-adverse-effect level (NOAEL) in rats and dogs following 90 min intravenous infusion of ONIVYDE once every 3 weeks for 18 weeks was at least 180 mg/m^2.
In safety pharmacology studies in dogs, ONIVYDE had no effect on cardiovascular, hemodynamic, electrocardiographic, or respiratory parameters at doses up to 21 mg/kg (420 mg/m^2). No findings indicative of CNS related toxicity were observed in the repeated dose toxicity studies in rats.

Genotoxic and carcinogenic potential

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

No carcinogenicity studies have been performed with ONIVYDE. For non-liposomal irinotecan, in rats treated once a week during 13 weeks at the maximum dose of 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.
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 must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
30 months.

After dilution
Chemical and physical stability for the diluted solution 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 and other handling

ONIVYDE 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 is recommended. If the solution contacts the skin, the skin should be washed immediately and thoroughly with soap and water. If the solution contacts mucous membranes, they should be flushed thoroughly with water. Pregnant staff should not handle ONIVYDE considering the cytotoxic nature of the medicinal product.

Preparation of the solution and administration

ONIVYDE is supplied as a sterile liposomal dispersion at a concentration of 5 mg/ml and must be diluted prior to administration. Dilute with 5% glucose solution for injection or sodium chloride 9 mg/ml (0.9%) solution for injection to prepare a solution of the appropriate dose of ONIVYDE diluted to a final volume of 500 ml. Mix the diluted solution by gentle inversion. The diluted solution is clear to slightly white to slightly opalescent and free from visible particles.

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

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

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

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1130/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 October 2016

10. DATE OF REVISION OF THE TEXT

01/2019

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.