APPROVED PIL

For

ONIVYDE

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Confidential Information

SERVIER LABORATORIES SOUTH AFRICA (PTY) LTD
3rd Floor, Building J, Hertford Office Park, 90 Bekker Road, Vorna Valley, Midrand, 1686, Republic of South Africa - Tel. +27 (0)861 700 900 - www.servier.co.za. DIRECTORS: P. Perez *, C.M ĚP Tartar *, C.G,P Sabathier *, *French. Reg. No. 1972/014307

Approved PIL	
Applicant	Servier Laboratories SA (Pty) Ltd
Product	**ONIVYDE**
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Patient Information Leaflet

ONIVYDE pegylated liposomal 4,3 mg/ml concentrate for dispersion for infusion

irinotecan

SCHEDULING STATUS S4

Read all of this leaflet carefully before you start receiving Onivyde

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist, nurse or other healthcare provider.
- **ONIVYDE** has been prescribed to you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

1. What ONIVYDE pegylated liposomal is and what it is used for

ONIVYDE pegylated liposomal is a cancer medicine that contains the active substance irinotecan. This active substance is held in tiny lipid (fatty) particles called liposomes.
Irinotecan belongs to a group of cancer medicines called 'topoisomerase inhibitors'. It blocks an enzyme called topoisomerase I, which is involved in the division of cell DNA. This prevents the cancer cells from multiplying and growing, and they eventually die.

The liposomes are expected to accumulate within the tumour and release the medicine slowly over time, thereby allowing it to act for longer.

ONIVYDE pegylated liposomal is used to treat adult patients with metastatic pancreatic cancer (cancer of the pancreas that has already spread elsewhere in the body) whose previously cancer treatment included a medicine called gemcitabine. **ONIVYDE** pegylated liposomal is used in combination with other cancer medicines, called 5-fluorouracil and leucovorin.
If you have any questions about how **ONIVYDE** pegylated liposomal works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you use ONIVYDE pegylated liposomal

Follow carefully all instructions given to you by your doctor. They may differ from the general information contained in this leaflet.

Do not use ONIVYDE pegylated liposomal

- if you have a history of a severe allergy to irinotecan, or any of the other ingredients of this medicine (listed in section 6).
- if you are breastfeeding.

Warnings and precautions

Talk to your doctor or nurse before you are given **ONIVYDE** pegylated liposomal.

- if you have ever had any liver problems or jaundice
- if you have ever had lung disease or have previously received medicines (colony stimulating factors) to increase your blood count or radiation therapy
- if you are taking other medicines (see section “Other medicines and **ONIVYDE** pegylated liposomal”)
- if you are planning to have a vaccination as many vaccinations must not be given during chemotherapy
- if you are on a controlled sodium diet as this medicine contains sodium.

Talk to your doctor or nurse immediately during treatment with **ONIVYDE** pegylated liposomal

- if you feel sudden shortness of breath, flushing, headache, skin rash or hives (itchy rash with swollen red bumps on the skin that appear suddenly), itching, swelling around the eyes, tightness in the chest or throat during or shortly after your infusion
- if you experience fever, chills or other symptoms of infection
- if you get diarrhoea with frequent liquid stools and cannot control this after 12 to 24 hours of treatment (see below)
- if you get breathlessness or cough.
- if you experience signs or symptoms of a blood clot, like sudden pain and swelling in a leg or an arm, sudden onset of coughing, chest pain or difficulty breathing.

What to do in case of diarrhoea

As soon as the first liquid stool occurs, start drinking large volumes of rehydration fluids (e.g. water, soda water, fizzy drinks, soup) to avoid losing too much liquid and salts from your body. Contact your doctor immediately to give you a suitable treatment. Your doctor may give you a medicine which contains loperamide to begin treatment at home but it must not be used for longer than 48 consecutive hours. If loose stools persist, contact your doctor.

Blood tests and medical examinations

Before you start treatment with **ONIVYDE** pegylated liposomal, your doctor will perform blood tests (or other medical examinations) to determine the best starting dose for you. You will need

to have further (blood or other) tests during treatment so that your doctor can monitor your blood cells and assess how you are responding to the treatment. Your doctor may need to adjust the dose or your treatment.

Children and adolescents

ONIVYDE pegylated liposomal is not recommended for use in adolescents and children below the age of 18 years.

Other medicines and ONIVYDE pegylated liposomal

Tell your doctor if you are taking, have recently taken or might take any other medicines.
It is especially important that you tell your doctor if you have been given irinotecan in any form earlier.
ONIVYDE pegylated liposomal must not be used instead of other medicines containing irinotecan because it behaves differently when it is contained in the liposomes than when it is given in its free form.

Tell your doctor, pharmacist or nurse if you are already having, or have recently had chemotherapy and/or radiotherapy or treatment with the antifungal medicine flucytosine.

It is also especially important that you tell your doctor if you are also taking the following medicines, since they reduce the level of irinotecan in your body:

- phenytoin, phenobarbital or carbamazepine (medicines used to treat convulsions and falls)
- rifampicin and rifabutin (medicines used to treat tuberculosis)
- St. John´s wort (a plant-based medicine used to treat depression and low mood).

It is especially important that you tell your doctor if you are also taking the following medicines, since they increase the level of irinotecan in your body:

- ketoconazole, itraconazole or voriconazole (medicines used to treat fungal infections)
- clarithromycin (an antibiotic medicine used to treat bacterial infections)
- indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, atazanavir (medicines against HIV infection)
- regorafenib (a medicine against certain forms of cancer)
- telaprevir (a medicine used to treat a liver disease called hepatitis C)
- nefazodone (a medicine used to treat depression, low mood)
- gemfibrozil (medicine used to treat high fat levels in the blood).

ONIVYDE pegylated liposomal with food, drink and alcohol

Avoid eating grapefruit and drinking grapefruit juice while you are receiving **ONIVYDE** pegylated liposomal as it may increase the level of irinotecan in your body.

Pregnancy, breastfeeding and fertility

You should not be given **ONIVYDE** pegylated liposomal if you are pregnant as it may harm the baby. Tell your doctor if you are or think you may be pregnant. Ask your doctor for advice if you are planning to have a baby. If you are given **ONIVYDE** pegylated liposomal you should not breast-feed until one month after the last dose.

Prior to taking this medicine talk with your doctor about the possible risk with this medicine and the options that may preserve your ability to have children.

During your **ONIVYDE** pegylated liposomal treatment and for seven months after you should choose an effective birth control method which suits you to prevent pregnancy in this period of time. Males should use condoms during **ONIVYDE** pegylated liposomal treatment and for 4 months thereafter.

Tell your doctor if you are breastfeeding. You must not be given **ONIVYDE** pegylated liposomal if you are breastfeeding your baby, as this may be harmful to your baby.

Driving and using machines

ONIVYDE pegylated liposomal may influence your ability to drive and use machines (as you may be sleepy, dizzy and exhausted with the use of **ONIVYDE** pegylated liposomal). You should avoid driving, using machines or performing other tasks that need full attention if you feel sleepy, dizzy and exhausted.

ONIVYDE pegylated liposomal contains sodium

This medicine contains 33,1 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 1,65 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How ONIVYDE pegylated liposomal is used

ONIVYDE pegylated liposomal must only be given by healthcare professionals trained in giving anticancer medicines.

Carefully follow all instructions given to you by your doctor or nurse.

Your doctor will decide upon the doses you will receive.

ONIVYDE pegylated liposomal is given as a drip (infusion) into a vein, which should take at least 90 minutes and should be given as a single dose.
After you have been given **ONIVYDE** pegylated liposomal you will be given two other medicines, leucovorin and 5-fluorouracil.
The treatment will be repeated every two weeks.
In certain cases, lower doses or longer dosing intervals may be required.
You may receive pre-medication against nausea and vomiting. If you have experienced sweating, abdominal cramping and salivation together with early frequent and liquid stools in previous treatments with **ONIVYDE** pegylated liposomal, you may receive additional medicines before **ONIVYDE** pegylated liposomal to prevent or reduce this in the following treament cycles.
If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

ONIVYDE can cause side effects.
Not all side effects reported for Triveram are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **ONIVYDE**, please consult your healthcare provider for advice.
Your doctor may also prescribe other medicines to help control your side effects.

Tell your doctor or nurse about any of the following serious side effects straight away

- if you experience swelling under the skin (angioedema) and/or symptoms of possible anaphylactic/anaphylactoid reactions such as sudden shortness of breath, flushing, nausea, headache, skin rash or hives (itchy rash with swollen red bumps on the skin that appear suddenly), itching, swelling around the eyes, and tightness in the chest or throat during the infusion or shortly after it. Severe allergic reactions may be life threatening. The infusion may need to be stopped and you may need to be treated or observed for the side effects
- if you get fever, chills and signs of an infection (as this might require immediate treatment)
- if you have severe persistent diarrhoea (liquid and frequent stools)—see section 2.

The following other side effects may occur

Frequent

- Low levels of white blood cells (neutropenia and leukopenia)
- Low level of red blood cells (anaemia)
- Low level of blood platelets (thrombocytopenia)
- Diarrhoea (loose or watery and frequent stools)
- Nausea and vomiting

- Pain in the stomach or in the gut area
- Sore mouth
- Loss of weight
- Loss of appetite
- Loss of body fluid (dehydration)
- Low level of salts (electrolytes) in the body (e.g. of potassium, magnesium)
- Unusual hair loss
- Tiredness
- Dizziness
- Swelling and fluid retention in the soft tissues (peripheral oedema)
- Soreness and swelling of the digestive tract lining (mucosal inflammation)
- Fever
- Generalised weakness
- Chills
- Infections, for example fungal infections in the mouth (oral candidiasis), fever with low counts of white blood cells (febrile neutropenia), infections related to the administration of the product into a vein
- Inflammation of the stomach and the guts (gastroenteritis)
- Systemic body inflammation, caused by infection (sepsis)
- Potentially life-threatening complication of whole body inflammation (septic shock)
- Infection of the lungs (pneumonia)
- Low level of white blood cells subtype, called lymphocytes with important function for the immune system (lymphopenia)
- Decrease in some salts (electrolytes) in the body (e.g. phosphate, sodium)
- Low blood sugar (hypoglycaemia)
- Sleeplessness
- Bad taste in the mouth
- A syndrome called cholinergic syndrome with sweating, salivation and abdominal cramping
- Low blood pressure (hypotension)
- Formation of a blood clot in a deep vein (deep vein thrombosis) or blockage of the main artery of the lung or one of its branches (pulmonary embolism), or blockage due to a blood clot elsewhere in the blood stream (embolism)
- Voice impairment, hoarse or excessively breathy voice
- Shortness of breath
- Inflammation in the gut
- Piles(haemorrhoids)

- Increases in liver enzymes (alanine aminotransferase or aspartate aminotransferase) in laboratory blood tests
- Increase in bilirubin levels (an orange-yellow pigment, waste product of the normal breakdown of the red blood cells) in other laboratory measurements related to liver function
- Increase in other laboratory measurements (increased international normalized ratio) related to the blood clotting system function
- Abnormally low blood levels of albumin (major protein in the body)
- Itching
- Sudden problems with kidney function which may lead to rapid deterioration or loss of the kidney function
- Abnormal reaction to the infusion causing symptoms like shortness of breath, flushing, headache, tightness in the chest or throat
- Abnormal fluid retention in the body causing swelling in the affected tissues (oedema).

Less Frequent

- Systemic body inflammation, caused by infection of the gall bladder and bile ducts (biliary sepsis)
- Allergic reaction to **ONIVYDE** pegylated liposomal (the active substance or the excipients)
- Diminished availability of oxygen to the body tissues
- Inflammation of the oesophagus (food pipe)
- Formation or presence of a blood clot within a blood vessel – vein or artery (thrombosis)
- Inflammation of the lining of the rectum (the end of the large intestine)
- Hives (swollen red bumps)
- Skin rash
- Type of rash, characterised by appearance of a flat, red area on the skin covered with bumps (maculo-papular rash)
- Change in the colour of the nail plates
- Reddening of the skin.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects to SAHPRA via **the "6.04 Adverse Drug Reaction Reporting Form"** found online under SAHPRA's publications https//www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of **ONIVYDE**.

5. How to store ONIVYDE pegylated liposomal

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

Store all medicine out of the sight of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after “EXP”. The expiry date refers to the last day of that month.

Do not freeze.

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

Once the concentrate has been diluted for infusion with 5% glucose solution for injection or sodium chloride 9 mg/ml (0.9 %) solution for injection, the dispersion should be used as soon as possible, but may be stored at ambient temperature (15 °C to 25 °C) for up to 6 hours. The diluted dispersion for infusion can be stored in the refrigerator (2 °C – 8 °C) for no more than 24 hours prior to use. It must be protected from light, and it must not be frozen.

Do not throw away this medicine via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ONIVYDE pegylated liposomal contains

- The active substance is irinotecan. One 10 ml vial of concentrate contains 43 mg irinotecan anhydrous free base (as sucrosofate salt in a pegylated liposomal formulation).
- The other ingredients are: 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); cholesterol, N-(carbonyl-methoxypolyethylene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE); sucrose octasulphate; 2- [4- (2-Hydroxyethyl)piperazin-1-yl]ethanesulfonic acid (HEPES buffer); sodium chloride and water for injections. **ONIVYDE** pegylated liposomal contains sodium, if you are on a controlled sodium diet, see section 2.

What ONIVYDE pegylated liposomal looks like and contents of the pack

ONIVYDE pegylated liposomal is supplied as a white to slightly yellow opaque isotonic liposomal dispersion in a glass vial.

Each pack contains one vial with 10 ml of concentrate.

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Holder of Certificate of Registration

Servier Laboratories SA (Pty) Ltd

3rd Floor, Building J

Hertford Office Park

90 Bekker Street

Vorna Valley

Midrand

2169

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