Package leaflet: Information for the user

ONIVYDE 5 mg/ml concentrate for solution for infusion
Pegylated liposomal irinotecan hydrochloride trihydrate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ONIVYDE is and what it is used for

What ONIVYDE is and how it works

ONIVYDE 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.

What ONIVYDE is used for

ONIVYDE 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 is used in combination with other cancer medicines, called 5-fluorouracil and leucovorin.

If you have any questions about how ONIVYDE works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you use ONIVYDE

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:

- 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
- 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")
- 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
- 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.

<u>What to do in case of diarrhoea</u>

As soon as the first liquid stool occurs, start drinking large volumes ofrehydration 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.

<u>Blood tests and medical examinations</u>

Before you start treatment with ONIVYDE, 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 stop treatment.

Children and adolescents

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

Other medicines and ONIVYDE

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 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.

It is also especially important that you tell your doctor if you are also taking the following medicines, since they reduce the availability of irinotecan in your body:
- phenytoin, phenobarbital or carbamazepin (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)
- as ONIVYDE should not be given to you together with this medicines.

It is especially important that you tell your doctor if you are also taking the following medicines, since they increase the availability 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)
- 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 with food and drink

Avoid eating grapefruits and drinking grapefruit juice while you are receiving ONIVYDE as it may increase the availability of the active substance of ONIVYDE in your body.

Pregnancy and breast-feeding

You should not be given ONIVYDE 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 you should not breast-feed until one month after the last dose.

During your ONIVYDE treatment and one month 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 treatment and 4 months thereafter.

Tell your doctor if you are breast-feeding. You must not be given ONIVYDE if you are breast-feeding as this may be harmful to your baby.

Driving and using machines

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

ONIVYDE contains sodium

One millilitre of this medicine contains 0.144 mmol (3.31 mg) sodium—keep this in mind if you are on a controlled sodium diet.

3. How ONIVYDE is used

ONIVYDE 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 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 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, you may receive additional medicines before ONIVYDE 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

Like all medicines, this medicine can cause side effects, although not everybody gets them. It is important that you are aware of what these side effects may be.

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 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, tightness in the chest or throat during the infusion or shortly after it (as 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 side effects may occur:

Very common (may affect more than 1 in 10 people)
- 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

Common (may affect up to 1 in 10 people)
- 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)
- 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)

Uncommon (may affect up to 1 in 100 people)
- Systemic body inflammation, caused by infection of the gall bladder and bile ducts (biliary sepsis)
- Allergic reaction to ONIVYDE (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)
- 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

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system below.

By reporting side effects you can help provide more information on the safety of this medicine.

United Kingdom

Yellow Card Svheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Gooogle Play or Apple App Store

5. How to store ONIVYDE

Keep this medicine out of the sight and reach 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.

Store in a refrigerator (2°C - 8°C).
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 solution 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 solution 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 contains

- The active substance is irinotecan hydrochloride trihydrate. One 10 ml vial of concentrate contains the equivalent of 50 mg irinotecan hydrochloride trihydrate (as the sucrosofate salt irinotecan sucrose octasulphate, in a pegylated liposomal formulation) which corresponds to 43 mg irinotecan.
- 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 contains sodium, if you are on a controlled sodium diet, see section 2.

What ONIVYDE looks like and contents of the pack

ONIVYDE 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.

Marketing Authorisation Holder
Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

Manufacturer
Les Laboratoires Servier Industrie
905, route de Saran
45520 Gidy
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

United Kingdom
Servier Laboratories Ltd
Tel: +44 (0)1753 666409

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

How to prepare and administer ONIVYDE

- 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 diluted solution by gentle inversion.
- ONIVYDE should be administered before leucovorin followed by 5-fluorouracil. 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.
- From a microbiological point of view, the product should be used as soon as possible after dilution. The diluted solution for infusion can be stored at ambient temperature (15°C to 25°C)for up to 6 hours or in the refrigerator (2ºC - 8ºC) for no more than 24 hours prior to use. It must be protected from light, and it must not be frozen.
- 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.

How to handle and dispose of ONIVYDE

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