Package leaflet: Information for the user

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

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 pegylated liposomal is and what it is used for

What ONIVYDE pegylated liposomal is and how it works

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.

What ONIVYDE pegylated liposomal is used for

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 cancer has not been previously treated or whose previous cancer treatment included a medicine called gemcitabine.

For patients whose cancer has not been previously treated, ONIVYDE pegylated liposomal is used in combination with other cancer medicines, called oxaliplatin, 5-fluorouracil and leucovorin.

For patients previously treated by 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 breast-feeding.

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

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

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.

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

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 (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 and drink

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

Pregnancy, breast-feeding 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 breast-feeding. You must not be given ONIVYDE pegylated liposomal if you are breast-feeding 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.
If your cancer has not been previously treated, after you have been given ONIVYDE pegylated liposomal you will be given three other medicines, oxaliplatin, leucovorin and 5-fluorouracil.
If your cancer has been previously treated with a medicine called gemcitabine, 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 treatment 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 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, 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:

Very common (may affect more than 1 in 10 people)
Laboratory test changes
- Low levels of white blood cells (neutropenia and leukopenia), Low level of red blood cells (anaemia)
- Low level of blood platelets (thrombocytopenia)
- Low level of salts in the body (e.g. of potassium, magnesium)

Stomach and gut
- Diarrhoea (loose or watery and frequent stools)
- Nausea and vomiting
- Pain in the stomach or in the gut area
- Sore mouth
- Soreness and swelling of the digestive tract lining (mucosal inflammation)

General
- Loss of weight
- Loss of appetite
- Loss of body fluid (dehydration)
- Tiredness and generalized weakness
- Abnormal fluid retention in the body causing swelling in the affected tissues (oedema)
- Fever

Skin
- Unusual hair loss

Nervous system
- Dizziness
- Nerve damage in arms and legs causing pain or numbness, burning and tingling (peripheral neuropathy)
- Paraesthesia, a sensation like numbness, tingling, pins and needles
- Bad taste in the mouth

Common (may affect up to 1 in 10 people)
Laboratory test changes
- Low level of white blood cells subtype, called lymphocytes with important function for the immune system (lymphopenia)
- Low blood sugar (hypoglycaemia)
- Abnormally low blood levels of albumin (major protein in the body)
- Increases in liver enzymes (alanine aminotransferase or aspartate aminotransferase or Gamma-glutamyltransferase) in laboratory blood tests
- High blood levels of alkaline phosphatase, a protein that helps specific chemical processes in the body found in many parts of your body. High alkaline phosphatase levels in your blood may be a sign of a liver or a bone disorder
- 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
- Increased blood creatinine, a product that shows that the kidneys are not functioning well

Stomach and gut
- Inflammation of the stomach and the guts (gastroenteritis)
- Inflammation in the gut (colitis), Inflammation of the bowel causing diarrhoea (Enterocolitis), Gas, Swelling in belly
- Indigestion
- Constipation
- Disease where stomach acid rises up into the oesophagus (Gastroesophageal reflux disease)
- Difficulty in swallowing (Dysphagia)
- Piles (haemorrhoids)

- Dry mouth

General
- Chills
- Sleeplessness
- Abnormal reaction to the infusion causing symptoms like shortness of breath, flushing, headache, tightness in the chest or throat
- Rapid heartbeat
- Blurry vision
- Headache

Skin
- Itching
- Dry skin
- Skin eruption
- Hand foot syndrome - redness, swelling, and/or pain on the palms of the hands and/or the soles of the feet
- Darker areas of skin (hyperpigmentation)

Nervous system
- A syndrome called cholinergic syndrome with sweating, salivation and abdominal cramping
- Toxicity causing neurological disorder
- Unpleasant and abnormal feeling when touched
- Shaking

Infections
- Infections, for example fungal infections in the mouth (oral candidiasis), fever with low counts of neutrophils in white blood cells (febrile neutropenia), infections related to the administration of the product into a vein
- Potentially life-threatening complication of whole body reaction to an infection (septic shock)
- Infection of the lungs (pneumonia)
- Infection of the urinary tract

Blood vessels
- Low blood pressure (hypotension)
- Thromboembolic events, formation of a blood clot in a blood vessel (vein or artery) 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)

Lungs and airways
- Voice impairment, hoarse or excessively breathy voice
- Shortness of breath
- Inflammation of the nose and throat
- Hiccups
- Nosebleed

Kidney
- Sudden problems with kidney function which may lead to deterioration or loss of the kidney function

Muscles
- Muscular weakness, Muscle pain, Abnormal muscle contractions

Uncommon (may affect up to 1 in 100 people)

Laboratory test changes
- Low levels of all types of blood cells (pancytopenia)
- Haemolytic anaemia, an excessive breakdown of red blood cells
- Monocyte count increased, increase in blood level of monocyte (a subtype of white blood cell)
- Increase in blood level of troponine I, a protein that tells if there is damage to your heart
- Protein total decreased, a decrease in blood protein level related to kidney or liver function or malabsorption
- Creatinine renal clearance decreased, a decreased level of creatinine clearance, showing that the kidneys are not working properly

- Excess protein in the urine
- Abnormal level of salts in the blood
- Low level of chlorine in the blood (hypochloremia)
- High levels of uric acid in the blood causing symptoms especially painful inflammation in the joints (Gout)
- High level of blood sugar (hyperglycaemia)
- Deficiency of Iron in the blood

Stomach and gut

- Inflammation of the oesophagus (food pipe)
- Inflammation of the lining of the rectum (the end of the large intestine)
- A blockage in the part of the gut leading out of the stomach (Duodenal obstruction)
- Abnormal muscle contractions in the oesophagus (tube that leads from the mouth to the stomach)
- Loss of movement in bowel muscles (Ileus paralytic)
- Lack of control over passing stools (Anal incontinence), Anal tear, Difficulty in pooping (pain, straining or obstructed defecation)
- Passage of blood through the anus path (Haematochezia)
- Rectal bleeding
- Painful sore inside of the mouth (Aphthous ulcer), Abnormal and unpleasant feeling in the mouth, Sensations like numbness, tingling, pins and needles in the mouth, Inflammation of corners of the mouth (or oral commissures), Loss or erosion of tissue of the mouth (mouth ulceration)
- Tongue disorder
- Dental caries, Gum disorder, Gum disease, Increased feeling or sensitivity of teeth, Serious inflammation of gums
- Stomach disorder, Inflammation of the stomach lining (Gastritis)
- Belching (eructation)
- Diverticulitis (a disease affecting the gut)

General

- Allergic reaction to the active substance or the excipients
- Eye irritation, Reduction of sharpness of vision, Conjunctivitis, a redness and discomfort in the eye
- Vertigo, a spinning sensation
- Feeling generally unwell (Malaise)
- General physical health deterioration
- Red, painful, and often swollen area on a part of body (Inflammation)
- Failure of one or more organs at the same time
- Temperature sensation abnormalities, Body's temperature measured below 35 °C (Hypothermia)
- Lip and face swelling
- Flu-like symptoms, such as high temperature, sore throat, runny nose, cough and chills
- Lack of proper nutrition
- Fluid retention around the tumor
- Excessive sweating
- Cold in the extremities

Skin

- Hives (swollen red bumps)
- Toxicity causing nail disorders, Change in the colour of the nail plates
- Skin lesion, Reddening of the skin (erythema), Dry skin, Sensitive skin
- Rash with blister-like lesions filled with pus (rash pustular)
- Inflammation of the skin with bullae (Dermatitis bullous)
- Dermatitis exfoliative generalised, flaking or peeling of the skin
- Petechiae, tiny blood spots under the skin and Telangiectasia, visible small linear red blood vessels
- Inflammatory disease causing red, scaly patches on the skin (Psoriasis)

- Dryness of vulva and vagina

Nervous system

- Seizure
- Bleeding inside the brain (Cerebral haemorrhage), Sudden interruption of blood flow in the brain caused by blocked blood supply to a part of the brain (Ischaemic stroke), Temporary interruption of blood flow in the brain (Transient ischaemic attack)
- Inability to smell (anosmia), Loss of taste functions of the tongue (ageusia)
- Feeling of unsteady or dizzy (balance disorder)
- Excessive sleepiness
- Reduced sensation to touch, pain and temperature
- Limitations in cognitive functioning and skills (Intellectual disability) and Unusual lack of energy and of mental acuteness (Lethargy)
- Reduced ability to memorize things
- Imminent, transient feeling of loss of consciousness (presyncope) and Fainting (syncope)
- Feeling of confusion
- Neurosis (a mental disorder with high levels of anxiety) and depression

Infections

- Systemic body inflammation, caused by infection of the gall bladder and bile ducts (biliary sepsis)
- Fever caused by infection
- Bacterial infection caused by a germ called Clostridium difficile
- Mucosal infection (Infection of the lining of body cavities)
- Furuncle (boil), a bacterial infection of hair follicles
- Infection of voice box (laryngitis)
- Sinusitis, an inflammation of sinuses
- Infection of tooth
- Fungal infection of the mouth
- Herpes simplex, Viral infection of the mouth (such as cold sores) or the genitals
- Mycotic infection of vulva and vagina
- Anal abscess, a swollen anal area where pus has collected

Lungs and airways

- Diminished availability of oxygen to the body tissues or Increased supply of oxygen to the body tissues and organs
- Cough
- Inflammation in the nose
- Collapse of the whole or part of a lung (atelectasis)
- Inflammation in the lungs (pneumonitis, interstitial lung disease)

Pain

- Pain, Non-cardiac chest pain, Pain in armpit area, Joint pain, Back pain, Bone pain, Pain in extremity, Pain and inflammation in several joints (Polyarthritis), Pain in mouth and throat (Oropharyngeal pain)
- Chest pain
- Pain in the mouth (Paraesthesia oral)
- Gum pain
- Painful urination

Heart and blood vessels

- Angina pectoris - Pains to the chest, jaw and back, brought on by physical effort and due to problems with the blood flow to the heart
- Heart attack
- A forceful heartbeat that may be rapid or irregular
- Abnormal electrical activity of the heart that affects its rhythm (Electrocardiogram QT prolonged)
- High blood pressure (hypertension)
- Inflammation of a vein (phlebitis)
- Collection of blood under the skin (Haematoma)

Liver
- Inflammation of the bile duct, usually caused by bacteria (Cholangitis)
- Inflammation of the liver in reaction to certain substances
- Reduced flow of bile from the liver because of a blockage (Cholestasis)
- Hepatic cytolysis, inflammation of the liver with increased blood levels of transaminases, blood chemicals from the liver that tell how liver is functioning

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet.
You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store ONIVYDE pegylated liposomal

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

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The following information is intended for healthcare professionals only:

How to prepare and administer ONIVYDE pegylated liposomal

- ONIVYDE pegylated liposomal is supplied as a sterile liposomal dispersion at a concentration of 4.3 mg/ml and must be diluted prior to administration using a needle not larger than 21 gauge. Dilute with 5% glucose solution for injection or sodium chloride 9 mg/ml (0.9%) solution for injection to prepare a dispersion of the appropriate dose of ONIVYDE pegylated liposomal diluted to a final volume of 500 ml. Mix diluted dispersion by gentle inversion.
- In first-line treatment of metastatic adenocarcinoma of the pancreas, ONIVYDE pegylated liposomal should be administered before oxaliplatin, followed by leucovorin followed by 5-fluorouracil.
- In treatment of metastatic adenocarcinoma of the pancreas in patients who have progressed following gemcitabine-based therapy, ONIVYDE pegylated liposomal should be administered before leucovorin followed by 5-fluorouracil.
- ONIVYDE pegylated liposomal must not be administered as a bolus injection or an undiluted dispersion.
- Aseptic techniques must be followed during the preparation of the infusion. ONIVYDE pegylated liposomal is for single use only.
- From a microbiological point of view, the product should be used as soon as possible after dilution. The diluted dispersion 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 pegylated liposomal

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