Package leaflet: Information for the user

Opdualag 240 mg/80 mg concentrate for solution for infusion
nivolumab/relatlimab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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.
- It is important that you keep the patient card with you at all times.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Opdualag is and what it is used for

Opdualag is a cancer medicine used to treat advanced melanoma (a type of skin cancer that can spread elsewhere in the body). It can be used in adults and in adolescents 12 years of age and older.

Opdualag contains two active substances: nivolumab and relatlimab. Both active substances are monoclonal antibodies, proteins designed to recognise and attach to a specific target substance in the body. Nivolumab attaches to a target protein called PD 1. Relatlimab attaches to a target protein called LAG-3.

PD 1 and LAG-3 can switch off the activity of T cells (a type of white blood cell that forms part of the immune system, the body's natural defences). By attaching to the two proteins, nivolumab and relatlimab block their actions and prevent them from switching off your T cells. This helps increase the T cell activity against the melanoma cancer cells.

2. What you need to know before you are given Opdualag

You should not be given Opdualag
- if you are allergic to nivolumab, relatlimab or any of the other ingredients of this medicine (listed in section 6). Talk to your doctor if you are not sure.

Warnings and precautions

Talk to your doctor before you get Opdualag as it may cause:
- Problems with your lungs such as breathing difficulties or cough. These may be signs of inflammation of the lungs (pneumonitis or interstitial lung disease).
- Diarrhoea (watery, loose or soft stools) or inflammation of the intestines (colitis) with symptoms such as stomach pain and mucus or blood in stool.

- Inflammation of the liver (hepatitis). Signs and symptoms of hepatitis may include abnormal liver function tests, eye or skin yellowing (jaundice), pain in the right side of your stomach area, or tiredness.
- Inflammation of or problems with your kidneys. Signs and symptoms may include abnormal kidney function tests, or decrease in amount of urine.
- Problems with your hormone producing glands (including the pituitary, thyroid and adrenal glands), which may affect how these glands work. Signs and symptoms that these glands are not working properly may include fatigue (extreme tiredness), weight change or headache and visual disturbances.
- Diabetes including a serious, sometimes life-threatening problem due to acid in the blood produced from diabetes (diabetic ketoacidosis). Symptoms may include feeling more hungry or thirsty than usual, need to urinate more often, weight loss, feeling tired or having difficulty thinking clearly, breath that smells sweet or fruity, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat, feeling sick or being sick, stomach pain, and deep or fast breathing.
- Inflammation of the skin that can lead to severe skin reaction (known as toxic epidermal necrolysis and Stevens-Johnson syndrome). Signs and symptoms of severe skin reaction may include rash, itching, and peeling of the skin (possibly fatal).
- Inflammation of the heart muscle (myocarditis). Signs and symptoms may include chest pain, irregular and/or rapid heartbeat, fatigue, swelling in the ankles or shortness of breath.
- Haemophagocytic lymphohistiocytosis. A rare disease in which your immune system makes too many otherwise normal infection-fighting cells called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, swollen lymph glands, breathing problems, easy bruising, kidney abnormalities, and heart problems.
- Solid organ transplant rejection.
- Graft-versus-host disease after stem cell transplantation (where the transplanted cells from a donor attack your own cells). If you have received one of these transplants, your doctor will consider whether you should receive treatment with Opdualag. Graft-versus-host disease can be severe and can lead to death.
- Infusion reactions, which may include shortness of breath, itching or rash, dizziness or fever.

Tell your doctor immediately if you have any of these signs or symptoms or if they get worse. Do not try to treat your symptoms with other medicines on your own. Your doctor may
- give you other medicines to prevent complications and reduce your symptoms,
- skip your next dose of Opdualag,
- or stop your treatment with Opdualag altogether.

Please note that these signs and symptoms are sometimes delayed and may develop weeks or months after your last dose. Before treatment, your doctor will check your general health. You will also have blood tests during your treatment.

Check with your doctor or nurse before you are given Opdualag if:
- you have an active autoimmune disease (a condition where the body attacks its own cells);
- you have melanoma of the eye;
- you have been told that your cancer has spread to your brain;
- you have been taking medicines to suppress your immune system.

Children and adolescents
Opdualag should not be used in children below 12 years of age.

Other medicines and Opdualag
Before you are given Opdualag, tell your doctor if you are taking any medicines that suppress your immune system, such as corticosteroids, since these medicines may interfere with the effect of Opdualag. However, once you are treated with Opdualag, your doctor may give you corticosteroids to reduce any possible side effects that you may have during your treatment.
Tell your doctor if you are taking, have recently taken or are planning to take any other medicines. Do not take any other medicines during your treatment without talking to your doctor first.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Do not use Opdualag if you are pregnant unless your doctor specifically tells you to. The effects of Opdualag in pregnant women are not known, but it is possible that the active substances, nivolumab and relatlimab, could harm an unborn baby.
- You must use effective contraception while you are being treated with Opdualag and for at least 5 months following the last dose of Opdualag, if you are a woman who could become pregnant.
- If you become pregnant while using Opdualag tell your doctor.

It is not known whether Opdualag can pass into breast milk and affect a baby that is breast-fed. Talk to your doctor about the benefits and risks before breast-feeding during or after treatment with Opdualag.

Driving and using machines
Opdualag has a minor influence on the ability to drive and use machines; however, use caution when performing these activities until you are sure that Opdualag does not adversely affect you.

Patient card
You will also find key messages from this package leaflet on the patient card you have been given by your doctor. It is important that you keep this patient card at all times and show it to your partner or caregivers.

3. How to use Opdualag

How much Opdualag is given
The recommended dose by infusion in adults and adolescents 12 years of age and older who weigh at least 30 kg is 480 mg nivolumab and 160 mg relatlimab every 4 weeks.

Depending on your dose, the appropriate amount of Opdualag may be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection before use. Opdualag may also be used undiluted.

How Opdualag is given
You will receive treatment with Opdualag in a hospital or clinic, under the supervision of an experienced doctor.

Opdualag will be given to you as an infusion (a drip) into a vein, every 4 weeks. Each infusion takes about 30 minutes to give.

Your doctor will continue treating you with Opdualag for as long as you keep benefitting from it or until side effects become too severe.

If you miss a dose of Opdualag
It is very important for you to keep all your appointments to receive Opdualag. If you miss an appointment, ask your doctor when to schedule your next dose.

If you stop using Opdualag
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with Opdualag unless you have discussed this with your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your doctor will discuss these with you and will explain the risks and benefits of your treatment.

Be aware of important symptoms of inflammation (described in section 2 under 'warnings and precautions'). Opdualag acts on your immune system and may cause inflammation in parts of your body. Inflammation may cause serious damage to your body and some inflammatory conditions may be life-threatening and need treatment or withdrawal of Opdualag.

The following side effects have been reported with Opdualag:

Very common (may affect more than 1 in 10 people)
- infection of the urinary tract (the parts of the body that collect and pass out urine)
- decreased number of red blood cells (which carry oxygen) and white blood cells (lymphocytes, neutrophils, leucocytes; which are important in fighting infection)
- underactive thyroid gland (which can cause tiredness or weight gain)
- decreased appetite
- headache
- difficulty breathing, cough
- diarrhoea (watery, loose or soft stools), vomiting; nausea; stomach pain; constipation
- skin rash (sometimes with blisters), skin colour change in patches (vitiligo), itching
- pain in the muscles, bones and joints
- feeling tired or weak, fever.

Changes in the results of tests carried out by your doctor may show:
- abnormal liver function (increased amounts of the liver enzymes alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase in your blood)
- abnormal kidney function (increased amounts of creatinine in your blood)
- decrease of sodium and magnesium, and decrease or increase of calcium and potassium.

Common (may affect up to 1 in 10 people)
- infections of the upper respiratory tract (nose and upper airways)
- decreased number of platelets (cells which help the blood to clot), increase in some white blood cells
- decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), inflammation of the pituitary gland situated at the base of the brain, overactive thyroid gland, inflammation of the thyroid gland
- high or low sugar levels in the blood; weight loss, high levels of the waste product uric acid in the blood, decreased levels of the protein albumin in the blood, dehydration
- state of confusion
- inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), dizziness, changes in the sense of taste
- inflammation of the eye (which causes pain and redness, vision problems or blurry vision), vision problems, dry eyes, excessive tear production
- inflammation of the heart muscle
- inflammation of a vein, which can cause redness, tenderness and swelling
- inflammation of the lungs (pneumonitis), characterised by coughing and difficulty breathing; nasal congestion (blocked nose)
- inflammation of the intestines (colitis), inflammation of the pancreas, inflammation of the stomach (gastritis), difficulty swallowing, mouth ulcers and cold sores; dry mouth
- inflammation of the liver (hepatitis)
- unusual hair loss or thinning (alopecia), isolated area of skin growth that becomes red and itchy (lichenoid keratosis), sensitivity to light, dry skin
- painful joints (arthritis), muscle spasms, muscle weakness
- kidney failure (changes in amount or colour of urine, blood in urine, swelling ankles, loss of appetite), high levels of proteins in the urine

- oedema (swelling), flu-like symptoms, chills
- reactions related to the administration of the medicine.

Changes in the results of tests carried out by your doctor may show:
- abnormal liver function (higher blood levels of the waste product bilirubin, higher blood levels of the liver enzyme gamma-glutamyl transferase)
- increase in sodium and magnesium
- increased level of troponin (a protein released into the blood when the heart is damaged)
- increased level of the enzyme that breaks down glucose (sugar) (lactate dehydrogenase), the enzyme that breaks down fats (lipase), the enzyme that breaks down starch (amylase)

Uncommon (may affect up to 1 in 100 people)
- inflammation and infection in the hair follicles
- disorder in which red blood cells are destroyed faster than they can be made (haemolytic anaemia)
- underactive function of the pituitary gland situated at the base of the brain; underactive function of the glands producing sex hormones
- inflammation of the brain, which may include confusion, fever, memory problems or seizures (encephalitis), a temporary inflammation of the nerves that causes pain, weakness, and paralysis in the extremities (Guillain-Barré syndrome), inflammation of the optic nerve that may cause a complete or partial loss of vision
- an inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada disease), red eye
- fluid around the heart
- asthma
- inflammation of the oesophagus (passage between throat and stomach)
- inflammation of the bile duct
- skin rashes and blistering on the legs, arms, and abdomen (pemphigoid), skin disease with thickened patches of red skin, often with silvery scales (psoriasis), hives (itchy, bumpy rash)
- inflammation of the muscles causing weakness, swelling, and pain, disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome), inflammation of muscles causing pain or stiffness, inflammation of the joints (painful joint disease), disease in which the immune system attacks its own tissues, causing widespread inflammation and tissue damage in the affected organs, such as joints, skin, brain, lungs, kidneys, and blood vessels (systemic lupus erythematosus)
- inflammation of the kidney
- absence of sperm in the semen.

Changes in the results of tests carried out by your doctor may show:
- increase in level of c-reactive protein
- red blood cell sedimentation rate increased.

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 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 Opdualag

Opdualag will be given to you in a hospital or clinic and the healthcare professionals will be responsible for its storage.

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 the vial label 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.
The unopened vial can be stored at controlled room temperature (up to 25 °C) for up to 72 hours.

Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What Opdualag contains

- The active substances are nivolumab and relatlimab.
  Each mL of concentrate for solution for infusion contains 12 mg of nivolumab and 4 mg of relatlimab.
  One vial of 20 mL concentrate contains 240 mg nivolumab and 80 mg relatlimab.

- The other ingredients are histidine, histidine hydrochloride monohydrate, sucrose, pentetic acid, polysorbate 80 (E433) and water for injections.

What Opdualag looks like and contents of the pack
Opdualag concentrate for solution for infusion (sterile concentrate) is a clear to opalescent, colourless to slightly yellow liquid that is essentially free of particles.
It is available in cartons containing one glass vial.

Marketing Authorisation Holder
Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer
Swords Laboratories Unlimited Company t/a Bristol-Myers Squibb Cruiserath Biologics
Cruiserath Road, Mulhuddart
Dublin 15, D15 H6EF
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The following information is intended for healthcare professionals only:

Opdualag is supplied as a single-dose vial and does not contain any preservatives. Preparation should be performed by trained personnel in accordance with good practice rules, especially with respect to asepsis.

Opdualag can be used for intravenous administration either:
- without dilution, after transfer to an infusion container using an appropriate sterile syringe; or
- after diluting according to the following instructions:
  - the final infusion concentration should range between 3 mg/mL nivolumab and 1 mg/mL relatlimab to 12 mg/mL nivolumab and 4 mg/mL relatlimab.
  - the total volume of infusion must not exceed 160 mL. For patients weighing less than 40 kg, the total volume of infusion should not exceed 4 mL per kilogram of patient weight.

Opdualag concentrate may be diluted with either:
- sodium chloride 9 mg/mL (0.9%) solution for injection; or
- 50 mg/mL (5%) glucose solution for injection.

Preparing the infusion
- Inspect the Opdualag concentrate for particulate matter or discolouration. Do not shake the vial. Opdualag is a clear to opalescent, colourless to slightly yellow solution. Discard the vial if the solution is cloudy, discoloured, or contains particulate matter.
- Withdraw the required volume of Opdualag concentrate using an appropriate sterile syringe and transfer the concentrate into a sterile, intravenous container (ethylvinyl acetate (EVA), polyvinyl chloride (PVC), or polyolefin). Each vial is filled with 21.3 mL of solution, which includes an overfill of 1.3 mL.
- If applicable, dilute Opdualag solution with the required volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. For ease of preparation, the concentrate can also be transferred directly into a pre-filled bag containing the appropriate volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.
- Gently mix the infusion by manual rotation. Do not shake.

Administration
Opdualag infusion must not be administered as an intravenous push or bolus injection.

Administer the Opdualag infusion intravenously over a period of 30 minutes.
Use of an infusion set and an in-line or add-on filter, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm) is recommended.

Opdualag infusion is compatible with EVA, PVC and polyolefin containers, PVC infusion sets and in-line filters with polyethersulfone (PES), nylon, and polyvinylidene fluoride (PVDF) membranes with pore sizes of 0.2 µm to 1.2 µm.

Do not co-administer other medicinal products through the same infusion line.
After administration of the Opdualag dose, flush the line with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.

Storage conditions and shelf life

Unopened vial
Opdualag must be **stored in a refrigerator** (2 °C to 8 °C). The vials must be kept in the original package in order to protect from light. Opdualag should not be frozen.
The unopened vial can be stored at controlled room temperature (up to 25 °C) for up to 72 hours.

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

After preparation of infusion
Chemical and physical in-use stability from the time of preparation has been demonstrated as follows (times are inclusive of the administration period):

Infusion preparation	**Chemical and physical in-use stability**	
	Storage at 2 °C to 8 °C protected from light	**Storage at room temperature (≤ 25 °C) and room light**
Undiluted or diluted with sodium chloride 9 mg/mL (0.9%) solution for injection	30 days	24 hours (of total 30 days storage)
Diluted with 50 mg/mL (5%) glucose solution for injection	7 days	24 hours (of total 7 days storage)

From a microbiological point of view, the prepared solution for infusion, regardless of the diluent, should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless preparation has taken place in controlled and validated aseptic conditions.

Disposal
Do not store any unused portion of the infusion solution for reuse. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.