OPDIVO 10 mg/mL concentrate for solution for infusion
nivolumab

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 Alert Card with you during treatment.
- 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 OPDIVO is and what it is used for
2. What you need to know before you use OPDIVO
3. How to use OPDIVO
4. Possible side effects
5. How to store OPDIVO
6. Contents of the pack and other information

1. What OPDIVO is and what it is used for

OPDIVO is a medicine used to treat:
- advanced melanoma (a type of skin cancer) in adults
- melanoma after complete resection in adults (treatment after surgery is called adjuvant therapy)
- advanced non-small cell lung cancer (a type of lung cancer) in adults
- advanced renal cell carcinoma (advanced kidney cancer) in adults
- classical Hodgkin lymphoma that has come back after or has not responded to previous therapies, including an autologous stem-cell transplant (a transplant of your own blood-producing cells) in adults
- advanced cancer of the head and neck in adults
- advanced urothelial carcinoma (bladder and urinary tract cancer) in adults.

It contains the active substance nivolumab, which is a monoclonal antibody, a type of protein designed to recognise and attach to a specific target substance in the body.

Nivolumab attaches to a target protein called programmed death-1 receptor (PD-1) that 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 PD-1, nivolumab blocks its action and prevents it from switching off your T cells. This helps increase their activity against the melanoma, lung, kidney, lymphoid, head and neck or bladder cancer cells.

OPDIVO may be given in combination with ipilimumab. It is important that you also read the package leaflet for this medicine. If you have any questions about ipilimumab, please ask your doctor.

2. What you need to know before you use OPDIVO
You should not be given OPDIVO
- if you are allergic to nivolumab or any of the other ingredients of this medicine (listed in section 6 "Contents of the pack and other information"). Talk to your doctor if you are not sure.

Warnings and precautions
Talk to your doctor before using OPDIVO as it may cause:
- Problems with your heart such as a change in the rhythm or rate of the heartbeat or an abnormal heart rhythm.
- 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 any symptoms of inflammation of the intestines (colitis), 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 on the right side of your stomach area, or tiredness.
- Inflammation or problems with your kidneys. Signs and symptoms may include abnormal kidney function tests, or decreased volume of urine.
- Problems with your hormone producing glands (including the pituitary, the thyroid, the parathyroid and adrenal glands) that 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, decreased blood levels of calcium and visual disturbances.
- Diabetes (symptoms include excessive thirst, the passing of a greatly increased amount of urine, increase in appetite with a loss of weight, feeling tired, drowsy, weak, depressed, irritable and generally unwell) or diabetic ketoacidosis (acid in the blood produced from diabetes).
- 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 muscles such as myocarditis (inflammation of the heart muscle), myositis (inflammation of the muscles) and rhabdomyolysis (stiffness in muscles and joints, muscle spasm). Signs and symptoms may include muscle pain, stiffness, weakness, chest pain, or severe fatigue.
- Solid organ transplant rejection.
- Graft-versus-host disease.

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 in order to prevent complications and reduce your symptoms,
- withhold the next dose of OPDIVO,
- or stop your treatment with OPDIVO 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 OPDIVO if:
- you have an autoimmune disease (a condition where the body attacks its own cells);
- you have melanoma of the eye;
- you were previously given ipilimumab, another medicine for treating melanoma, and experienced serious side effects because of that medicine;
- you have been told that your cancer has spread to your brain;
- you have any history of inflammation of the lungs;
- you have been taken medicines to suppress your immune system.

Complications of stem cell transplant that uses donor stem cells (allogeneic) after treatment with OPDIVO. These complications can be severe and can lead to death. Your healthcare provider will monitor you for signs of complications if you have an allogeneic stem cell transplant.
Children and adolescents
OPDIVO should not be used in children and adolescents below 18 years of age.

Other medicines and OPDIVO
Before you are given OPDIVO, 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 OPDIVO. However, once you are treated with OPDIVO, your doctor may give you corticosteroids to reduce any possible side effects that you may have during your treatment and this will not impact the effect of the medicine.

Tell your doctor if you are taking or have recently taken any other medicines. Do not take any other medicines during your treatment without talking to your doctor first.

Pregnancy and breast-feeding
Tell your doctor if you are pregnant or think you might be, if you are planning to become pregnant, or if you are breast-feeding.

Do not use OPDIVO if you are pregnant unless your doctor specifically tells you to. The effects of OPDIVO in pregnant women are not known, but it is possible that the active substance, nivolumab, could harm an unborn baby.

- You must use effective contraception while you are being treated with OPDIVO and for at least 5 months following the last dose of OPDIVO, if you are a woman who could become pregnant.
- If you become pregnant while using OPDIVO tell your doctor.

It is not known whether nivolumab gets into breast milk. A risk to the breast-fed infant cannot be excluded. Ask your doctor if you can breast-feed during or after treatment with OPDIVO.

Driving and using machines
Nivolumab is unlikely to affect your ability to drive or use machines; however, use caution when performing these activities until you are sure that nivolumab does not adversely affect you.

OPDIVO contains sodium
Tell your doctor if you are on a low-sodium (low-salt) diet before you are given OPDIVO. This medicine contains 2.5 mg sodium per mL of concentrate.

You will also find this information in the Patient Alert Card you have been given by your doctor. It is important that you keep this Alert Card and show it to your partner or caregivers.

3. How to use OPDIVO

How much OPDIVO is given
When OPDIVO is given on its own, the recommended dose is either 240 mg given every 2 weeks or 480 mg given every 4 weeks depending on indication.

When OPDIVO is given on its own for the treatment of melanoma after complete resection in adults, the recommended dose is 3 mg of nivolumab per kilogram of your body weight every 2 weeks.

When OPDIVO is given in combination with ipilimumab for the treatment of skin cancer, the recommended dose of OPDIVO is 1 mg of nivolumab per kilogram of your body weight for the first 4 doses (combination phase). Thereafter the recommended dose of OPDIVO is 240 mg given every 2 weeks or 480 mg given every 4 weeks (single-agent phase).

When OPDIVO is given in combination with ipilimumab for the treatment of advanced kidney cancer, the recommended dose of OPDIVO is 3 mg of nivolumab per kilogram of your body weight for the first 4 doses (combination phase). Thereafter, the recommended dose of OPDIVO is 240 mg given every 2 weeks or 480 mg given every 4 weeks (single-agent phase).
Depending on your dose, the appropriate amount of OPDIVO will be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection before use. More than one vial of OPDIVO may be necessary to obtain the required dose.

**How OPDIVO is given**

You will receive treatment with OPDIVO in a hospital or clinic, under the supervision of an experienced doctor.

OPDIVO will be given to you as an infusion (a drip) into a vein (intravenously) over a period of 30 or 60 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving. Your doctor will continue giving you OPDIVO for as long as you keep benefitting from it or until you no longer tolerate the treatment.

When OPDIVO is given in combination with ipilimumab, you will be given an infusion over a period of 30 minutes, every 3 weeks for the first 4 doses (combination phase). Thereafter it will be given as an infusion over a period of 30 or 60 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving (single-agent phase).

**If you miss a dose of OPDIVO**

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

**If you stop using OPDIVO**

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

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

When OPDIVO is given in combination with ipilimumab, you will first be given OPDIVO followed by ipilimumab.

Please refer to the package leaflet of ipilimumab in order to understand the use of this medicine. If you have questions about this medicine, please 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.** OPDIVO 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 nivolumab.

The following side effects have been reported with **nivolumab alone:**

**Very common (may affect more than 1 in 10 people)**
- Decrease in some white blood cells
- Diarrhoea (watery, loose or soft stools), nausea
- Skin rash sometimes with blisters, itching
- Feeling tired or weak

**Common (may affect up to 1 in 10 people)**
- Infections of the upper respiratory tract
- Allergic reaction, reactions related to the infusion of the medicine
- Underactive thyroid gland (which can cause tiredness or weight gain), overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss)
- Decreased appetite
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), headache, dizziness
- High blood pressure (hypertension)
- Inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), shortness of breath (dyspnoea), cough
- Inflammation of the intestines (colitis), mouth ulcers and cold sores (stomatitis), vomiting, stomach pain, constipation, dry mouth
- Skin colour change in patches (vitiligo), dry skin, redness of the skin, unusual hair loss or thinning
- Pain in the muscles, bones (musculoskeletal pain) and joints (arthralgia)
- Fever, oedema (swelling)

Uncommon (may affect up to 1 in 100 people)
- Serious lung infection (pneumonia), bronchitis
- Increase in some white blood cells
- Decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain, swelling of the thyroid gland, diabetes
- Dehydration, increased acid levels in the blood
- Inflammation of the liver (hepatitis)
- Damage to nerves causing numbness and weakness (polyneuropathy), inflammation of the nerves caused by the body attacking itself, causing numbness, weakness, tingling or burning pain (autoimmune neuropathy)
- Inflammation of the eye (which causes pain and redness), blurred vision, dry eyes
- Fast heart rate, inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders)
- Fluid around the lungs
- Inflammation of the pancreas (pancreatitis), inflammation of the stomach (gastritis)
- Severe condition of the skin that causes red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body (erythema multiforme), skin disease with thickened patches of red skin, often with silvery scales (psoriasis), skin condition of the face where the nose and cheeks are unusually red (rosacea), hives (itchy, bumpy rash)
- Inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica), inflammation of the joints (arthritis)
- Inflammation of the kidney, kidney failure (including abrupt loss of kidney function)
- Pain, chest pain

Rare (may affect up to 1 in 1000 people)
- A disease causing the inflammation or enlargement of a lymph node (Kikuchi lymphadenitis)
- Life-threatening allergic reaction
- Acid in the blood produced from diabetes (diabetic ketoacidosis)
- Blockage of bile ducts
- A temporary inflammation of the nerves that causes pain, weakness, and paralysis in the extremities (Guillain- Barré syndrome), loss of the protective sheath around nerves (demyelination), a condition in which the muscles become weak and tire easily (myasthenic syndrome)
- Inflammation of the brain
- Changes in the rhythm or rate of the heartbeat, abnormal heart rhythm, inflammation of the heart muscle
- Inflammatory disease of blood vessels
- Fluid in the lungs
- Ulcer of the small intestines
- Severe and possibly fatal peeling of the skin (toxic epidermal necrolysis or Stevens-Johnson syndrome)
Disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren’s syndrome), aching muscles, muscle tenderness or weakness, not caused by exercise (myopathy), inflammation of the muscles (myositis), stiffness in muscles and joints, muscle spasm (rhabdomyolysis)

The following side effects have been reported with nivolumab in combination with ipilimumab:

**Very common (may affect more than 1 in 10 people)**
- Underactive thyroid gland (which can cause tiredness or weight gain), overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss)
- Decreased appetite
- Headache
- Shortness of breath (dyspnoea)
- Inflammation of the intestines (colitis), diarrhoea (watery, loose or soft stools), vomiting, nausea, stomach pain
- Skin rash sometimes with blisters, itching
- Pain in the joints (arthralgia), pain in the muscles and bones (musculoskeletal pain)
- Feeling tired or weak, fever

**Common (may affect up to 1 in 10 people)**
- Serious lung infection (pneumonia), infections of the upper respiratory tract, inflammation of the eye (conjunctivitis)
- Increase in some white blood cells
- Allergic reaction, reactions related to the infusion of the medicine
- Decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain, swelling of the thyroid gland, diabetes
- Dehydration
- Inflammation of the liver
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), dizziness
- Inflammation of the eye (which causes pain and redness), blurred vision
- Fast heart rate
- High blood pressure (hypertension)
- Inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), fluid around the lungs, blood clots, cough
- Mouth ulcers and cold sores (stomatitis), inflammation of the pancreas (pancreatitis), constipation, dry mouth
- Skin colour change in patches (vitiligo), dry skin, redness of the skin, unusual hair loss or thinning, hives (itchy rash)
- Inflammation of the joints (arthritis), muscle spasm, muscle weakness
- Kidney failure (including abrupt loss of kidney function)
- Oedema (swelling), pain, chest pain, chills

**Uncommon (may affect up to 1 in 100 people)**
- Bronchitis
- Temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord (aseptic meningitis)
- Chronic diseases associated with a build-up of inflammatory cells in various organs and tissues, most commonly the lungs (sarcoidosis)
- Increased acid levels in the blood
- Acid in the blood produced from diabetes (diabetic ketoacidosis)
- A temporary inflammation of the nerves that causes pain, weakness and paralysis in the extremities (Guillain-Barré syndrome); damage to nerves causing numbness and weakness (polyneuropathy); inflammation of the nerves; foot drop (peroneal nerve palsy); inflammation of the nerves caused by the body attacking itself, causing numbness, weakness, tingling or burning
pain (autoimmune neuropathy); muscle weakness and tiredness without atrophy (myasthenia gravis)

- Inflammation of the brain
- Changes in the rhythm or rate of the heartbeat, abnormal heart rhythm, inflammation of the heart muscle
- Intestinal perforation, inflammation of the stomach (gastritis), inflammation of the duodenum
- Skin disease with thickened patches of red skin, often with silvery scales (psoriasis), severe condition of the skin that causes red, often itchy spots, similar to the rash of measles, which starts on the limbs and sometimes on the face and the rest of the body (erythema multiforme)
- Severe and possibly fatal peeling of the skin (Stevens-Johnson syndrome)
- Chronic disease of joints (spondyloarthropathy), disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren’s syndrome), aching muscles, muscle tenderness of weakness, not caused by exercise (myopathy), inflammation of the muscles (myositis), stiffness in muscles and joints, muscle spasm (rhabdomyolysis), inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica)
- Inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders)
- Decreased function of the parathyroid gland
- Chronic diseases associated with a build-up of inflammatory cells in various organs and tissues, most commonly the lungs (sarcoidosis)
- Temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord (aseptic meningitis)

Tell your doctor immediately if you get any of the side effects listed above. Do not try to treat your symptoms with other medicines on your own.

Changes in test results
OPDIVO alone or in combination with ipilimumab may cause changes in the results of tests carried out by your doctor. These include:

- Abnormal liver function tests (increased amounts of the liver enzymes aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase in your blood, higher blood levels of the waste product bilirubin)
- Abnormal kidney function tests (increased amounts of creatinine in your blood)
- High (hyperglycaemia) or low (hypoglycaemia) sugar levels in the blood
- A decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- An increased level of the enzyme that breaks down fats and of the enzyme that breaks down starch
- Increased or decreased amount of calcium or potassium
- Increased or decreased blood levels of magnesium or sodium
- Decrease in body weight

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via (see details below). By reporting side effects you can help provide more information on the safety of this medicine.
5. **How to store OPDIVO**

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 to 8°C).
Do not freeze.
Store in the original package in order to protect from light.
The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 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 OPDIVO contains**

- The active substance is nivolumab.
  Each mL of concentrate for solution for infusion contains 10 mg of nivolumab.
  Each vial contains either 40 mg (in 4 mL), 100 mg (in 10 mL) or 240 mg (in 24 mL) of nivolumab.

- The other ingredients are sodium citrate dihydrate, sodium chloride (see section 2 "OPDIVO contains sodium"), mannitol (E421), pentetic acid, polysorbate 80, sodium hydroxide, hydrochloric acid and water for injections.

**What OPDIVO looks like and contents of the pack**

OPDIVO concentrate for solution for infusion (sterile concentrate) is a clear to opalescent, colourless to pale yellow liquid that may contain few light particles.

It is available in packs containing either 1 vial of 4 mL, 1 vial of 10 mL or 1 vial of 24 mL.

Not all pack sizes may be marketed.
Preparation and administration of OPDIVO

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

Calculating the dose

More than one vial of OPDIVO concentrate may be needed to give the total dose for the patient.

Nivolumab monotherapy:
The prescribed dose for the patient is 240 mg or 480 mg given regardless of body weight depending on indication.

Nivolumab monotherapy (for the adjuvant treatment of melanoma) or nivolumab in combination with ipilimumab:
The prescribed dose for the patient is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given.
The total nivolumab dose in mg = the patient’s weight in kg × the prescribed dose in mg/kg.
The volume of OPDIVO concentrate to prepare the dose (mL) = the total dose in mg, divided by 10 (the OPDIVO concentrate strength is 10 mg/mL).

Preparing the infusion

Take care to ensure aseptic handling when you prepare the infusion.

OPDIVO 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 1 and 10 mg/mL.
  - the total volume of infusion must not exceed 160 mL. For patients weighing less than 40 kg, the total volume of infusion must not exceed 4 mL per kilogram of patient weight.

- OPDIVO 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.

STEP 1
- Inspect the OPDIVO concentrate for particulate matter or discoloration. Do not shake the vial. OPDIVO concentrate is a clear to opalescent, colourless to pale yellow liquid. Discard the vial if the solution is cloudy, is discoloured, or contains particulate matter other than a few translucent-to-white particles.
- Withdraw the required volume of OPDIVO concentrate using an appropriate sterile syringe.

STEP 2
- Transfer the concentrate into a sterile, evacuated glass bottle or intravenous container (PVC or polyolefin).
- If applicable, dilute 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 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

OPDIVO infusion must not be administered as an intravenous push or bolus injection. Administer the OPDIVO infusion intravenously over a period of 30 or 60 minutes depending on the dose.

OPDIVO infusion should not be infused at the same time in the same intravenous line with other agents. Use a separate infusion line for the infusion.

Use an infusion set and an in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm).

OPDIVO infusion is compatible with:
- PVC containers
- Polyolefin containers
- Glass bottles
- PVC infusion sets
- In-line filters with polyethersulfone membranes with pore sizes of 0.2 µm to 1.2 µm.

After administration of the nivolumab 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
OPDIVO 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. OPDIVO should not be frozen. The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours.

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

OPDIVO infusion
OPDIVO infusion must be completed within 24 hours of preparation. If not used immediately, the solution may be stored under refrigeration conditions (2°C-8°C) and protected from light for up to 24 hours [a maximum of 8 hours of the total 24 hours can be at room temperature (20°C-25°C) and room light]. Other in-use storage time and conditions are the responsibility of the user.

**Disposal**
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.