Package leaflet: Information for the user

OPDIVO 300 mg solution for injection
OPDIVO 600 mg solution for injection
nivolumab

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 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

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)
- non-small cell lung cancer (a type of lung cancer) prior to resection or prior to and after resection in adults (treatment prior to surgery is called neoadjuvant therapy; 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
- advanced cancer of the head and neck in adults
- advanced urothelial carcinoma (bladder and urinary tract cancer) in adults
- urothelial carcinoma after complete resection in adults
- advanced colorectal cancer (colon or rectal cancer) in adults
- advanced oesophageal cancer (gullet cancer) in adults
- oesophageal (gullet) or gastro-oesophageal junction cancer with residual disease after chemoradiation followed by surgery in adults
- advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma (stomach or gullet cancer) in adults.
- unresectable or advanced hepatocellular carcinoma (liver 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, head and neck, bladder and urinary tract, colon, rectal, stomach, oesophageal or gastro-oesophageal junction cancer cells.

OPDIVO may be given in combination with other anti-cancer medicines. It is important that you also read the package leaflet for these other medicines. If you have any questions about these medicines, 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** 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 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.**
- **Haemophagocytic lymphohistiocytosis**. A rare disease in which our immune system makes too many of otherwise normal infection fighting cells called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems.
- **Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome:** an overlap of either two or three conditions including inflammation of the heart muscle (myocarditis) that may cause chest pain, shortness of breath, irregular and/or rapid heartbeat, inflammation of the muscles (myositis) that may cause muscle pain, and a condition that may cause muscle weakness and tiredness (myasthenia gravis).

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 taking **medicines to suppress your immune system.**

OPDIVO acts on your immune system. It may cause inflammation in parts of your body. Your risk of these side effects may be higher if you already have an autoimmune disease (a condition where the body attacks its own cells). You may also experience frequent flares of your autoimmune disease, which in the majority of cases are mild.

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 solution for injection 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 OPDIVO 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
OPDIVO or OPDIVO in combination with ipilimumab may have a minor influence on the ability to drive and use machines; however, use caution when performing these activities until you are sure that OPDIVO does not adversely affect you.

OPDIVO contains polysorbate 80 (E433)

This medicine contains 1.25 mg of polysorbate 80 in each 2.5 mL and 2.5 mg of polysorbate 80 in each 5 mL vial which is equivalent to 5 mg/10 mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

You will also find key messages from this package leaflet in the patient card you have been given by your doctor. It is important that you keep this patient 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 as an injection under your skin (subcutaneous injection), the recommended dose is either 600 mg given every 2 weeks or 1200 mg given every 4 weeks.

When OPDIVO is given intravenously 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 given as an injection under your skin is 600 mg every 2 weeks or 1200 mg every 4 weeks (single-agent phase).

When OPDIVO is given intravenously 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 given as an injection under your skin is 600 mg every 2 weeks or 1200 mg every 4 weeks (single-agent phase).

When OPDIVO is given intravenously in combination with ipilimumab for the treatment of advanced colon or rectal cancer, the recommended dose of OPDIVO is 3 mg of nivolumab per kilogram of your body weight or 240 mg for the first 4 doses (combination phase) depending on your treatment. Thereafter, the recommended dose of OPDIVO is 600 mg every 2 weeks or 1200 mg every 4 weeks (single-agent phase) given as an injection under your skin, depending on your treatment.

When OPDIVO is given in combination with ipilimumab for the treatment of unresectable or advanced liver cancer, the recommended dose of OPDIVO given as an infusion into a vein is 1 mg of nivolumab per kilogram of your body weight for up to 4 doses (combination phase) depending on your treatment. Thereafter, the recommended dose of OPDIVO given as an injection under your skin is 600 mg every 2 weeks or 1200 mg every 4 weeks (single-agent phase) depending on your treatment

When OPDIVO is given in combination with chemotherapy for the neoadjuvant treatment (before surgery) of non-small cell lung cancer, the recommended dose of OPDIVO given as an injection under your skin is 900 mg every 3 weeks for 3 cycles.

When OPDIVO is given in combination with chemotherapy for the neoadjuvant (before surgery) and adjuvant (after surgery) treatment of non-small cell lung cancer, the recommended dose of OPDIVO given as an injection under your skin is 900 mg every 3 weeks for 4 cycles (combination phase) prior to resection and 1200 mg every 4 weeks (single-agent phase) as an injection under your skin.

When OPDIVO is given in combination with chemotherapy for the treatment of advanced oesophageal cancer, the recommended dose of OPDIVO is 600 mg every 2 weeks or 1200 mg every 4 weeks as an injection under your skin.

When OPDIVO is given in combination with chemotherapy for the treatment of advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, the recommended dose of OPDIVO is either 600 mg every 2 weeks or 900 mg every 3 weeks as an injection under your skin.

When OPDIVO is given in combination with chemotherapy for the treatment of urothelial carcinoma (bladder and urinary tract cancer), the recommended dose of OPDIVO is 900 mg every 3 weeks as an

injection under your skin, for up to 6 cycles. Thereafter, the recommended dose of OPDIVO is 600 mg every 2 weeks or 1200 mg every 4 weeks (single agent phase) given as an injection under your skin.

When OPDIVO is given in combination with cabozantinib for the treatment of advanced kidney cancer, the recommended dose of OPDIVO is 600 mg given every 2 weeks or 1200 mg given every 4 weeks as an injection under your skin.

More than one vial of OPDIVO may be necessary to obtain the required dose.

How OPDIVO is given
You will receive treatment with OPDIVO under the supervision of an experienced doctor.

OPDIVO is given as an injection under the skin (subcutaneously) of the abdomen or thigh over a period of 3 to 5 minutes, every 2 weeks, 3 weeks, or 4 weeks, depending on the dose you are receiving. Treatment with OPDIVO will continue for as long as you keep benefitting from it or until you no longer tolerate the treatment.

When OPDIVO is given intravenously in combination with ipilimumab for the treatment of skin, advanced kidney, advanced colon or rectal cancer, or unresectable or advanced liver cancer, you will be given an infusion over a period of 30 minutes, every 3 weeks for the first 4 doses (combination phase) depending on your treatment. Thereafter, OPDIVO will be given as an injection under the skin of the abdomen or thigh over a period of 3 to 5 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving (single-agent phase).

When OPDIVO is given as an injection under the skin of the abdomen or thigh in combination with chemotherapy for the neoadjuvant (before surgery) treatment of non-small cell lung cancer it will be given over a period of 3 to 5 minutes, every 3 weeks. After surgery, OPDIVO will be given as an injection under the skin of the abdomen or thigh over a period of 3 to 5 minutes, every 4 weeks, depending on the dose you are receiving (single agent phase).

When OPDIVO is given as an injection under the skin of the abdomen or thigh in combination with chemotherapy for the treatment of advanced oesophageal cancer, OPDIVO will be given over a period of 3 to 5 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving.

When OPDIVO is given in combination with chemotherapy for the treatment of urothelial carcinoma (bladder or urinary tract cancer), OPDIVO will be given as an injection under the skin of the abdomen or thigh over a period of 3 to 5 minutes, every 3 weeks (combination phase), and then it will be given every 2 or 4 weeks, depending on the dose you are receiving (single-agent phase).

When OPDIVO is given as an injection under the skin of the abdomen or thigh in combination with chemotherapy for the treatment of advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma, it will be given over a period of 3 to 5 minutes every 2 weeks or 3 weeks, depending on the dose you are receiving.

When OPDIVO is given as an injection under the skin of the abdomen or thigh in combination with cabozantinib, it will be given over a period of 3 to 5 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving.

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 other anti-cancer medicines, you will first be given OPDIVO followed by the other medicine.

Please refer to the package leaflet of these other medicines in order to understand the use of these medicines. If you have questions about them, 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 OPDIVO.

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

Very common (may affect more than 1 in 10 people)
- Infections of the upper respiratory tract
- 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)
- Decreased appetite, high sugar levels in the blood (hyperglycaemia)
- Headache
- Shortness of breath (dyspnoea), cough
- Diarrhoea (watery, loose or soft stools), vomiting, nausea, stomach pain, constipation
- Skin rash sometimes with blisters, itching
- Pain in the muscles, bones (musculoskeletal pain) and joints (arthralgia)
- Feeling tired or weak, fever

Common (may affect up to 1 in 10 people)
- Serious lung infection (pneumonia), bronchitis
- Reactions related to the infusion of the medicine, allergic reaction, (including life-threatening allergic reaction)
- Underactive thyroid gland (which can cause tiredness or weight gain), overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss), swelling of the thyroid gland
- Dehydration, decrease in body weight, low sugar levels in the blood (hypoglycaemia)
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), dizziness
- Blurred vision, dry eyes
- Fast heart rate, abnormal heart rhythm
- High blood pressure (hypertension)
- Inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), fluid around the lungs
- Inflammation of the intestines (colitis), mouth ulcers and cold sores (stomatitis), dry mouth
- Skin colour change in patches (vitiligo), dry skin, redness of the skin, unusual hair loss or thinning
- Inflammation of the joints (arthritis)
- Kidney failure (including abrupt loss of kidney function)
- Pain, chest pain, oedema (swelling)
- Reaction at site of injection

Uncommon (may affect up to 1 in 100 people)
- Increase in some white blood cells
- Chronic diseases associated with a build-up of inflammatory cells in various organs and tissues, most commonly the lungs (sarcoidosis)

- 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, diabetes
- Increased acid levels in the blood (metabolic acidosis)
- 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)
- Inflammation of the heart muscle, inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders), changes in the rhythm or rate of the heartbeat
- Fluid in the lungs
- Inflammation of the pancreas (pancreatitis), inflammation of the stomach (gastritis)
- Inflammation of the liver (hepatitis), blockage of bile ducts (cholestasis)
- 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), hives (itchy, bumpy rash)
- Inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica)
- Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome: an overlap of either two or three conditions, including inflammation of the heart muscle (myocarditis), inflammation of the muscles (myositis), and a condition that may cause muscle weakness and tiredness (myasthenia gravis)

Rare (may affect up to 1 in 1000 people)
- A temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord (aseptic meningitis)
- A disease causing the inflammation or enlargement of a lymph node (Kikuchi lymphadenitis)
- Acid in the blood produced from diabetes (diabetic ketoacidosis), decreased function of the parathyroid gland
- 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)
- An inflammation of the optic nerve that may cause a complete or partial loss of vision (optic neuritis)
- Inflammation of the brain
- Inflammatory disease of blood vessels
- Ulcer of the small intestines
- Severe and possibly fatal peeling of the skin (toxic epidermal necrolysis or Stevens-Johnson syndrome), skin condition of the face where the nose and cheeks are unusually red (rosacea)
- 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)
- Inflammation of the kidney, inflammation of the bladder, signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen
- Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)
- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):
- A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis)

- Solid organ transplant rejection
- A group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome)
- An inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome)
- Pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation (myelitis/transverse myelitis)
- Changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (lichen sclerosus or other lichen disorders)

The following side effects have been reported **with OPDIVO in combination with other anti-cancer medicines** (the frequency and severity of side effects may vary with the combination of anti-cancer medicines received):

Very common (may affect more than 1 in 10 people)
- Infections of the upper respiratory tract
- 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)
- 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, decrease in body weight, high (hyperglycaemia) or low (hypoglycaemia) sugar levels in the blood
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), headache, dizziness, altered sense of taste
- High blood pressure (hypertension)
- Shortness of breath (dyspnoea), cough, abnormal speaking sound (dysphonia)
- Diarrhoea (watery, loose or soft stools), constipation, vomiting, nausea, stomach pain, mouth ulcers and cold sores (stomatitis), indigestion (dyspepsia)
- Skin rash sometimes with blisters, itching, pain of the hands or soles of the feet: rash or redness of the skin, tingling and tenderness developing to symmetrical redness, swelling and pain primarily on the palm of the hand and sole of the foot (palmar-plantar erythrodysaesthaesia syndrome)
- Pain in the joints (arthralgia), pain in the muscles and bones (musculoskeletal pain), muscle spasm
- Excess protein in urine
- Feeling tired or weak, fever, oedema (swelling)

Common (may affect up to 1 in 10 people)
- Serious lung infection (pneumonia), bronchitis, inflammation of the eye (conjunctivitis)
- Increase in some white blood cells, decrease in neutrophils with fever
- Allergic reaction (including life-threatening 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, decreased levels of albumin in the blood, decreased levels of phosphate in the blood
- Sensations like numbness and tingling (paraesthesia)
- Hearing a persistent sound in your ear when no sound exists (tinnitus)
- Blurred vision, dry eye
- Fast heart rate, abnormal heart rhythm
- Formation of a blood clot within a blood vessel (thrombosis), inflammatory disease of blood vessels
- Inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), fluid around the lungs, blood clots, nose bleeding

- Inflammation of the intestines (colitis), inflammation of the pancreas (pancreatitis), dry mouth, inflammation of the stomach (gastritis), oral pain, haemorrhoids (piles)
- Inflammation of the liver
- Skin colour change in patches (including vitiligo), redness of the skin, unusual hair loss or thinning, hair colour change, hives (itchy rash), discolouration or abnormal darkening of the skin (skin hyperpigmentation), dry skin
- Inflammation of the joints (arthritis), muscle weakness, aching muscles
- Kidney failure (including abrupt loss of kidney function)
- Pain, chest pain, chills
- Feeling generally unwell (malaise)

Uncommon (may affect up to 1 in 100 people)
- Acid in the blood produced from diabetes (diabetic ketoacidosis)
- Increased acid levels in the blood
- 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); 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 or syndrome)
- Inflammation of the brain
- Inflammation of the eye (which causes pain and redness)
- Changes in the rhythm or rate of the heartbeat, slow heart rate, inflammation of the heart muscle
- Intestinal perforation, inflammation of the duodenum, burning or painful sensation in the tongue (glossodynia)
- Severe and possibly fatal peeling of the skin (Stevens-Johnson syndrome), 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), changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (other lichen disorders)
- Muscle tenderness or weakness, not caused by exercise (myopathy), inflammation of the muscles (myositis), stiffness in muscles and joints, inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica), bone damage in the jaw, abnormal opening between two body parts, such as an organ or blood vessel and another structure (fistula)
- Inflammation of the kidney, inflammation of the bladder, signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen
- Myocarditis-Myositis-Myasthenia Gravis Overlap Syndrome: an overlap of either two or three conditions, including inflammation of the heart muscle (myocarditis), inflammation of the muscles (myositis), and a condition that may cause muscle weakness and tiredness (myasthenia gravis)

Rare (may affect up to 1 in 1000 people)
- 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)
- Decreased function of the parathyroid gland
- A group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome)
- An inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome)
- An inflammation of the optic nerve that may cause a complete or partial loss of vision (optic neuritis)
- Inflammation of the nerves

- Pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation (myelitis/transverse myelitis)
- Severe and possibly fatal peeling of the skin (toxic epidermal necrolysis), changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (lichen sclerosus)
- 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), muscle spasm (rhabdomyolysis)
- Lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)
- Coeliac disease (characterised by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods)

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):
- A condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis)
- Solid organ transplant rejection
- Inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders)

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 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, gamma-glutamyltransferase, 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)
- 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
- Increased amount of thyroid stimulating hormone
- Increase in blood triglyceride levels in the blood
- Increase in cholesterol levels in the blood

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme, Website:
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 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.

Do not store any unused portion of the injection 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 solution for injection contains 120 mg of nivolumab.
Each 2.5 mL vial contains 300 mg of nivolumab.
Each 5 mL vial contains 600 mg of nivolumab.

- The other ingredients are recombinant human hyaluronidase (rHuPH20), histidine, histidine hydrochloride monohydrate, sucrose, pentetic acid, polysorbate 80 (E433), methionine, and water for injection (see section 2 "OPDIVO contains polysorbate 80 (E433)").

What OPDIVO looks like and contents of the pack
OPDIVO solution for injection is a clear to opalescent, colourless to pale yellow liquid that may contain few light particles.

It is available in packs containing either 1 glass vial of 2.5 mL or 1 glass vial of 5 mL.

Not all pack sizes may be marketed

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
Ireland

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The following information is intended for healthcare professionals only:

To prevent medication errors, it is important to check the vial labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) is being given to the patient as prescribed.

<u>Preparation and administration of OPDIVO</u>

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 may be needed to give the total dose for the patient.

Nivolumab monotherapy
The prescribed dose for the patient is 600 mg or 1200 mg given regardless of body weight.

Nivolumab in combination with chemotherapy in neoadjuvant treatment of non-small cell lung cancer
The prescribed dose for the patient is 900 mg given regardless of body weight.

Neoadjuvant and adjuvant treatment of non-small cell lung cancer
The prescribed dose for the patient is 900 mg given regardless of body weight administered in combination with platinum-based chemotherapy (neoadjuvant phase). Then, after surgery (adjuvant phase), the prescribed dose for the patient is 1200 mg as monotherapy (single-agent phase) given regardless of body weight.

Nivolumab in combination with chemotherapy in advanced oesophageal cancer
The prescribed dose for the patient is 600 mg or 1200 mg given regardless of body weight.

Nivolumab in combination with chemotherapy in gastric, gastro-oesophageal junction or oesophageal adenocarcinoma
The prescribed dose for the patient is 600 mg or 900 mg given regardless of body weight.

Nivolumab in combination with chemotherapy in urothelial carcinoma
The prescribed dose for the patient is 900 mg (combination phase) or 600 mg or 1200 mg (single-agent phase) given regardless of body weight.

Nivolumab in combination with cabozantinib in advanced kidney cancer
The prescribed dose for the patient is nivolumab 600 mg or 1200 mg given regardless of body weight.

Preparing the injection
- Inspect the vial of OPDIVO solution for injection for particulate matter or discolouration. Do not shake the vial. OPDIVO solution for injection is a clear to opalescent, colourless to yellow liquid. Discard the vial if the solution is cloudy, is discoloured, or contains particulate matter other than a few translucent-to-white particles.
- Allow the vial or vials (depending on the prescribed dose) to reach room temperature.
- Withdraw the required volume of OPDIVO solution for injection using an appropriate sterile syringe and transfer needle.

Administration
OPDIVO solution for injection must not be administered intravenously.

Administer the OPDIVO solution for injection subcutaneously via a 23G-25G hypodermic needle or subcutaneous administration set (e.g., winged/butterfly) **over a period of 3 to 5 minutes** into the subcutaneous tissue of the abdomen or thigh.

Alternate injection sites for successive injections. Do not inject into areas where the skin is tender, red, or bruised, or areas where there are scars or moles. If the administration is interrupted, continue administering at the same site, or at an alternate site.

Do not administer other subcutaneous medications at the same site used for OPDIVO solution for injection.

OPDIVO solution for injection is compatible with:
- Polypropylene
- Polycarbonate
- Polyethylene
- Polyurethane

- Polyvinyl chloride
- Fluorinated ethylene propylene
- Stainless steel

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.

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.

Storage in the syringe
From a microbiological point of view, once transferred from the vial to the syringe, the medicinal product should be used immediately since the medicine does not contain any antimicrobial-preservative or bacteriostatic agents. If not used immediately, OPDIVO solution for injection transferred to the syringe can be stored in the refrigerator at 2°C to 8°C, protected from light for up to 7 days and/or at room temperature 20°C to 25°C and room light for up to 8 hours. Discard if storage time exceeds these limits. Aseptic handling should be ensured during the preparation of the syringe for injection.

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