

PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986
The medicine is dispensed with a doctor's prescription only

OPDIVO®

Concentrate for solution for intravenous infusion

The active ingredient and its concentration:

nivolumab 10 mg/ml

For the list of inactive ingredients and allergens, please see section 2 under 'Important information about some of this medicine's ingredients' and section 6 'Further information'.

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

If the treating doctor prescribes you OPDIVO in combined treatment with ipilimumab, carefully read the patient leaflet that comes with ipilimumab as well. If the treating doctor prescribes you OPDIVO in combined treatment with cabozantinib, carefully read the patient leaflet that comes with cabozantinib as well. This medicine has been prescribed for the treatment of your ailment. Do not pass it on to others. It may harm them, even if it seems to you that their ailment is similar.

This leaflet does not take the place of talking with your treating doctor about your medical condition or your treatment.

Patient pocket guide and patient safety information card

In addition to the leaflet, patient pocket guide and patient safety information card are available for OPDIVO.

The pocket guide and the card contain important safety information which you have to know before and during the treatment with OPDIVO, and which you must follow. Review the patient pocket guide, the patient safety information card and the patient leaflet before you start using the medicine. Keep the card and the pocket guide for further review if required.

1. WHAT IS THIS MEDICINE INTENDED FOR?

OPDIVO is used to treat:

• **A type of skin cancer called melanoma**

- OPDIVO used alone or in combination with ipilimumab is indicated for treatment of adults and children 12 years of age and older with advanced (unresectable or metastatic) melanoma.
- OPDIVO is indicated as complementary (adjuvant) treatment for adults and children 12 years of age and older with Stage IIB, IIC, III or IV melanoma after complete resection.

• **Non-small cell lung cancer**

- OPDIVO, in combination with platinum-doublet chemotherapy, is indicated as treatment before surgery (neoadjuvant) of adult patients with resectable (tumors ≥ 4 cm or involve lymph nodes) non-small cell lung cancer.
- OPDIVO, in combination with ipilimumab and 2 treatment cycles of combined platinum-containing chemotherapy (platinum-doublet chemotherapy), is indicated as first-line treatment for adults with metastatic or recurrent non-small cell lung cancer with no changes in the EGFR or ALK genes in the tumor.
- OPDIVO is indicated for treatment of adults with metastatic non-small cell lung cancer whose disease has progressed during treatment or after treatment with platinum-based chemotherapy.

• **Malignant pleural mesothelioma, cancer of mesothelial cells comprising the pleura (lining of the lungs)**

OPDIVO in combination with ipilimumab is indicated as first-line treatment for adults with unresectable malignant pleural mesothelioma.

• **Advanced renal cell carcinoma**

- OPDIVO in combination with ipilimumab is indicated as first-line treatment for adults with advanced renal cell carcinoma at moderate or high risk.
- OPDIVO in combination with cabozantinib is indicated as first-line treatment for adults with advanced renal cell carcinoma.
- OPDIVO used alone is indicated for the treatment of adults with advanced renal cell carcinoma who have received prior anti-angiogenic therapy.

• **Classical Hodgkin lymphoma (a type of blood cancer)**

OPDIVO is indicated for treatment of adults with classical Hodgkin lymphoma that has come back or spread after:

- a stem cell transplant that uses your own stem cells (autologous), and treatment with brentuximab vedotin medicine or
- 3 or more systemic treatment lines including a stem cell transplant that uses your own stem cells (autologous).

• **Squamous cell head and neck cancer (squamous cell carcinoma)**

OPDIVO is indicated for treatment of adults with recurrent or metastatic squamous cell head and neck cancer whose disease has progressed during or following platinum-based chemotherapy.

• **Urothelial carcinoma (urinary tract or bladder cancer)**

OPDIVO is indicated as complementary (adjuvant) treatment for adults with urinary tract or bladder cancer at high risk of disease recurrence after radical tumor resection.

- OPDIVO, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma.

- OPDIVO is indicated for treatment of adults with locally advanced or metastatic urinary tract or bladder cancer:

- after their disease has progressed during or following platinum-based chemotherapy.
- after their disease has progressed during 12 months following platinum-based chemotherapy given prior to tumor resection surgery (neoadjuvant) or as complementary (adjuvant) therapy post-surgery.

• **Metastatic colon or rectal cancer (colorectal cancer)**

OPDIVO used alone or in combination with ipilimumab is indicated for treatment of adults and children aged 12 years and older with metastatic colorectal cancer expressing dMMR (mismatch repair deficient) or MSI-H (microsatellite instability-high), whose disease has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan.

• **Liver cancer (hepatocellular carcinoma)**

OPDIVO in combination with ipilimumab is indicated for the treatment of adults with liver cancer with mild liver impairment (Child-Pugh A) following treatment with sorafenib.

• **Esophageal cancer**

- OPDIVO is indicated for the complementary (adjuvant) treatment after complete resection of esophageal cancer or gastroesophageal junction cancer with residual pathological disease in adults treated with chemoradiotherapy (CRT) prior to resection.

- OPDIVO, in combination with fluoropyrimidine and platinum-based combination chemotherapy, is indicated for the first-line treatment of adult patients with unresectable, advanced, recurrent or metastatic esophageal squamous cell carcinoma with PD-L1 expression in ≥ 1% of the tumor cells.

- OPDIVO, in combination with ipilimumab, is indicated for the first-line treatment of adult patients with unresectable, advanced, recurrent or metastatic esophageal squamous cell carcinoma with PD-L1 expression in ≥ 1% of the tumor cells.

- OPDIVO is indicated for treatment of adults with unresectable, advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior treatment with fluoropyrimidine and platinum-based chemotherapy.

• **Gastric cancer, gastroesophageal junction cancer and esophageal adenocarcinoma**

OPDIVO in combination with fluoropyrimidine and platinum containing chemotherapy is indicated for treatment of adults with unresectable, advanced or metastatic gastric cancer, gastroesophageal junction cancer or esophageal adenocarcinoma.

Therapeutic group: antineoplastic agent.

2. BEFORE USING THE MEDICINE:

Do not use this medicine if:

- you are sensitive (allergic) to the active ingredient (nivolumab) or to any of the other ingredients in this medicine (see section 6).

Special warnings regarding use of this medicine

Before treatment with OPDIVO, tell the doctor about all of your medical conditions, including if:

- you have problems involving the immune system such as Crohn's disease, ulcerative colitis, or lupus
- you have had an organ transplant, including corneal transplant
- you have received or are about to receive a stem cell transplant that uses donor stem cells (allogeneic)
- you have received radiation treatment to your chest area in the past and have received other medicines that are like OPDIVO
- you have a condition that affects your nervous system, such as severe muscle weakness (myasthenia gravis) or Guillain-Barré syndrome
- you are pregnant or plan to become pregnant (see the section 'Pregnancy and breastfeeding')

- you are breastfeeding or plan to breastfeed (see the section 'Pregnancy and breastfeeding')

Children and adolescents:

There is no information regarding the efficacy and safety of OPDIVO:

- in children below the age of 12 with melanoma or metastatic colorectal cancer expressing dMMR or MSI-H, or
- in children for the treatment of other cancer types

Tests and follow up:

- The treating doctor will perform blood tests to monitor side effects.

Drug interactions:

If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist.

Pregnancy and breastfeeding

OPDIVO may harm your unborn baby.

Women who are able to become pregnant:

- The treating doctor should perform a pregnancy test before you start receiving OPDIVO.
- You should use an effective method of birth control during treatment and for 5 months after receiving the last dose of OPDIVO. Consult your treating doctor about birth control methods that you can use during this time.
- Tell the treating doctor right away if you become pregnant during treatment with OPDIVO.

Breastfeeding:

Do not breastfeed during treatment with OPDIVO and for 5 months after taking the last dose of OPDIVO. It is not known whether OPDIVO can pass into your breast milk.

Driving and operating machinery

Exercise caution when driving or using any tools or machines until you are certain that OPDIVO does not adversely affect you as a result of potential side effects (see section 4).

Children should be warned against riding bicycles or playing near the road, etc.

Important information about some of this medicine's ingredients

OPDIVO contains sodium.

If you consume a low sodium (low salt) diet, inform your doctor prior to administration of this medicine.

The medicine contains 2.5 mg sodium (the major ingredient of cooking salt/table salt) per each ml of the concentrated solution.

The medicine contains 10 mg sodium in each 4 ml vial. This quantity is equivalent to 0.5% of the recommended maximal daily dietary intake of sodium for an adult.

The medicine contains 25 mg sodium in each 10 ml vial. This quantity is equivalent to 1.5% of the recommended maximal daily dietary intake of sodium for an adult.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the medicine according to the doctor's instructions.

Check with your doctor or pharmacist if you are not sure about the dose or about how to take this medicine.

The dosage and treatment regimen will be determined only by the doctor.

- OPDIVO is administered by healthcare professionals directly into the vein through an intravenous (IV) line over 60 minutes or 30 minutes, depending on the dosage and frequency determined by the doctor.

- When OPDIVO is used alone, it is usually given every 2 weeks or every 4 weeks depending on the dose you are receiving.

- When OPDIVO is used in combination with ipilimumab, except for treating metastatic non-small cell lung cancer and for treating some cases of malignant pleural mesothelioma (see below), OPDIVO is usually given every 3 weeks for a total of 4 treatment doses. Ipilimumab will be given on the same day. After that, OPDIVO will be given alone every 2 weeks or every 4 weeks depending on the dose you are receiving.

- For treatment of non-small cell lung cancer before surgery (neoadjuvant), OPDIVO is given with a chemotherapy combination (platinum-containing chemotherapy and another chemotherapy medicine) every 3 weeks for 3 treatment cycles.

- For treatment of metastatic non-small cell lung cancer that has spread to other parts of your body, when OPDIVO is used in combination with ipilimumab, OPDIVO is given every 3 weeks, and ipilimumab is given every 6 weeks for up to 2 years. You will also need to receive chemotherapy every 3 weeks for 2 treatment cycles.

- For treatment of malignant pleural mesothelioma, OPDIVO is given every 2 weeks or every 3 weeks and ipilimumab is given every 6 weeks for up to 2 years.
- For treatment of advanced renal cell carcinoma, when OPDIVO is used in combination with cabozantinib, OPDIVO is usually given every 2 weeks or every 4 weeks depending on the dose you are receiving. Cabozantinib is given once daily by mouth.

- For metastatic or unresectable urothelial carcinoma, when OPDIVO is given in combination with chemotherapy medicines cisplatin and gemcitabine, OPDIVO is given every 3 weeks for up to 6 treatment cycles. Chemotherapy will be given on the same day. After that, OPDIVO will be given alone every 2 weeks or 4 weeks depending on the dose you are receiving.

- When OPDIVO is used in combination with fluoropyrimidine and platinum-based chemotherapy for treating esophageal squamous cell carcinoma, OPDIVO is given every 2 weeks or every 4 weeks for up to 2 years.
- When OPDIVO is used in combination with ipilimumab for treating esophageal squamous cell carcinoma, OPDIVO is given every 2 weeks or every 3 weeks and ipilimumab is given every 2 weeks or up to 2 years.

- For treatment of gastric cancer, gastroesophageal junction cancer and esophageal adenocarcinoma, when OPDIVO is given in combination with fluoropyrimidine and platinum containing chemotherapy, OPDIVO is given every 2 weeks or every 3 weeks depending on the dose you are receiving for up to 2 years. Chemotherapy will be given on the same day.

- The treating doctor will decide how many treatments you need.

- If you are unable to come in for your scheduled treatment, or if you forget to come in for treatment, contact the treating doctor as soon as possible to schedule a new appointment for treatment.

Do not exceed the recommended dose.

Adhere to the treatment regimen as recommended by the doctor.

If you have taken an overdose, or if a child has accidentally swallowed some medicine, refer immediately to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

Do not take medicines in the dark! Check the label and dose every time you take a medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of OPDIVO may cause side effects in some users. Do not be alarmed by the list of side effects. You may not suffer from any of them.

OPDIVO may cause serious side effects, including:

Severe side effects related to immune system activity

OPDIVO is a medicine that treats certain types of cancer by activating your immune system. OPDIVO may cause your immune system to attack healthy tissues and organs in any area of your body and can affect the way they work. These problems may sometimes become serious or life-threatening and may lead to death. These problems may appear at any time during treatment or even after treatment has ended. You may experience more than one of these problems at the same time.

Some of these problems may happen more often when OPDIVO is used in combination with additional treatment.

Immediately contact the treating doctor if you experience any new signs or symptoms or worsening signs or symptoms, including:

Lung problems.

- cough
- shortness of breath
- chest pain

Intestinal problems.

- diarrhea (loose stools) or more frequent bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdominal) pain or tenderness

Liver problems.

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of the stomach area (abdomen)
- dark urine (tea colored)
- bleeding or bruising more easily than normal

Hormone glands problems.

- headaches that will not go away or unusual headaches
- eye sensitivity to light

- you are breastfeeding or plan to breastfeed (see the section 'Pregnancy and breastfeeding')
- rapid heartbeat
- increased sweating
- extreme tiredness

- weight gain or weight loss
- feeling more thirsty or hungry than usual
- urinating more often than usual
- hair loss

- feeling cold
- constipation
- voice changes and gets deeper and lower

- dizziness or fainting

- changes in mood or behavior, such as decreased sex drive, irritability or forgetfulness

Kidney problems.

- decrease in your amount of urine
- blood in your urine

- swelling of your ankles
- loss of appetite

Skin problems.

- rash
- itching
- skin blistering or skin peeling
- swollen lymph nodes
- painful sores or ulcers in mouth or nose, throat, or genital area
- fever or flu-like symptoms

Problems may also happen in other organs and tissues. These are not all of the signs and symptoms of immune system problems that may happen with OPDIVO. Contact the treating doctor right away for any new or worsening signs or symptoms, which may include:

- chest pain, irregular heartbeat, shortness of breath or swelling of ankles
- confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs
- double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight
- severe or persistent muscle pain or weakness, muscle cramps
- low red blood cells count, predisposition to bruising

Rejection of a transplanted organ or tissue. Your doctor will tell you what signs and symptoms you should report and will monitor you depending on the type of organ transplant that you have had.

Getting medical treatment right away may help prevent these problems from becoming more serious.

The treating doctor will check you for these problems during treatment with OPDIVO. The doctor may treat you with corticosteroids or hormone replacement medicines. If the side effects are severe, the doctor may delay or completely stop treatment with OPDIVO.

Severe infusion-related side effects

Tell your treating doctor or nurse immediately if you experience any of the symptoms listed below when receiving the OPDIVO infusion:

- chills or shaking
- itching or rash
- flushing
- shortness of breath or wheezing
- dizziness

- feel like passing out

- back or neck pain

Complications of stem cell transplantation using donor stem cells (allogeneic).

These complications may be serious and may lead to death. These complications may happen if the transplantation was performed either before or after treatment with OPDIVO. Your treating doctor will monitor you for signs of complications if you have undergone an allogeneic stem cell transplant.

Additional side effects:

Side effects of OPDIVO when used alone including:

Very common side effects, affect more than 1 in 10 users:

- feeling tired
- weakness, generally feeling unwell
- fever

- swelling (edema), including swelling of the hands, ankles or feet (peripheral edema)

- diarrhea
- nausea
- vomiting
- constipation
- dyspepsia
- difficulty swallowing

- rash
- itching, including widespread itching

- vittigo, a disease in which light patches appear on the skin

- erythema manifested by skin redness and inflammation

- pain in muscles, bones, and joints

- headache

- dizziness

- upper respiratory tract infection

- nasal congestion

- pneumonia, including pneumonia involving the bronchi

- cough, cough with phlegm

- shortness of breath, shortness of breath upon exertion

- decreased appetite

- decreased weight

- back pain

- low thyroid hormone levels [hypothyroidism (decreased activity of the thyroid gland)] that can cause fatigue and weight gain

- high thyroid hormone levels [hyperthyroidism (increased activity of the thyroid gland)] that can cause rapid heart rate, sweating and weight loss

- thyroid gland problems, including thyroid gland inflammation (thyroiditis)

- abnormal renal function

- urinary tract infection

- liver inflammation (hepatitis)

- high blood pressure
- high level of sugar in blood (hyperglycemia)

- difficulty sleeping

- numbness, pain, tingling or burning in the hands or feet (peripheral neuropathy)

- abnormal laboratory test results

- infusion-related reactions

Common side effects, affect 1-10 in 100 users:

- irregular heartbeat

- inflammation of the eye iris and ciliary body (iridocyclitis)

- inflammation of the nerves manifested by numbness, weakness, tingling, or pain accompanied by burning sensation (sensory and peripheral neuropathy)

- intestinal perforation

- ulcers or sores in the mouth (stomatitis)

- severe skin condition that causes red, sometimes 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 inflammation of the skin manifested by redness and peeling of extensive skin areas (exfoliative dermatitis)

- psoriasis

- accumulation of fluid in the pleural cavity around the lungs (pleural effusion) which may cause shortness of breath and sometimes also chest pain and fever

- pulmonary embolism (blood clot in the lungs)

- inflammation of the lung tissues (pneumonitis) characterized by coughing and difficulty breathing, shortness of breath and cough

- interstitial lung disease characterized by shortness of breath and dry cough, and causing lung scarring

- respiratory failure (extreme difficulty breathing)

- acute renal injury

- sepsis

- general health condition deterioration

- intestinal obstruction (small intestine obstruction)

- inflammation of the colon (colitis)

- nerve inflammation (neuritis)
- paralysis of the fibular nerve in the leg characterized by pain in the calf, decreased sensation or numbness, muscle weakness, and in severe cases foot drop or typical limping (peroneal nerve palsy)

- respiratory tract infection

- feeling more thirsty or hungry than usual

- muscles inflammation (myositis)

- Sjogren's syndrome, a disease in which the immune system attacks mainly lacrimal and salivary glands

- chronic joints inflammation usually involving the spinal joints

- chronic joints inflammation usually involving the spinal joints (spondyloarthropathy)

Uncommon side effects, affect 1-10 patients in 1,000 users:

- low blood pressure

- adrenal glands insufficiency (decrease in the level of hormones secreted by adrenal glands located above the kidneys)

- sudden death

- gastrointestinal bleeding

- swelling of your arms (extreme difficulty breathing)

- esophageal fistula

Side effects occurring when OPDIVO is administered in combination with ipilimumab include:

Very common side effects, affect more than 1 in 10 users:

- feeling tired

- fever
- swelling (edema)

- rash
- itching, widespread itching

- dry skin

- diarrhea

- nausea

- vomiting