PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

nedicine is dispensed with a doctor's prescription only

OPDIVO®

Concentrate for solution for intravenous infusion

The active ingredient and its concentration:

For the list of inactive ingredients and allergens, please see section 2 under '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 pharmacist. 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.

pass it on to others. It may harm them, even if it seems to you that their ailment 5 months after receiving the last dose of OPDIVO. Consult your treating doctor This leaflet does not take the place of talking with your treating doctor about your • Tell the treating doctor right away if you become pregnant during treatment 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 quide, 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 of this medicine. treatment of adults and children 12 years of age and older with advanced inresectable 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 for an adult. (tumors ≥ 4 cm or involve lymph nodes) non-small cell lung cancer. OPDIVO, in combination with ipilimumab and 2 treatment cycles of combined num-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 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

OPDIVO is indicated for treatment of adults with locally advanced or metastatic urinary tract or bladder cancer: o 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 cancer with residual pathological disease in adults treated with adiotherapy (CRT) prior to resection.

combination chemotherapy, is indicated for the first-line treatment of adult

If you have further questions regarding use of the medicine, consult the

• abnormal laboratory test results patients with unresectable, advanced, recurrent or metastatic esophageal doctor or pharmacist. quamous 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

Gastric cancer, gastroesophageal junction cancer and esophageal

o OPDIVO is indicated for treatment of adults with unresectable, advanced, treatment with fluoropyrimidine and platinum-based chemotherapy.

adenocarcinoma OPDIVO in combination with fluoropyrimidine and platinum containing or metastatic gastric cancer, gastroesophageal junction cancer or esophageal problems at the same time.

Therapeutic group: antineoplastic agent. 2. BEFORE USING THE MEDICINE:

Do not use this medicine if:

adenocarcinoma.

• 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 • yellowing of your skin or the whites of your eyes stem cells (allogeneic) • you have received radiation treatment to your chest area in the past and have
• pain on the right side of the stomach area (abdomen)

received other medicines that are like OPDIVO • you have a condition that affects your nervous system, such as severe muscle • bleeding or bruising more easily than normal weakness (myasthenia gravis) or Guillain-Barré syndrome

• you are pregnant or plan to become pregnant (see the section 'Pregnancy and

• you are breastfeeding or plan to breastfeed (see the section 'Pregnancy and • eye problems

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

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

· voice changes and gets deeper and lower If you are taking, or have recently taken, other medicines, including dizziness or fainting non-prescription medicines and nutritional supplements, tell the doctor or • changes in mood or behavior, such as decreased sex drive, irritability or forgetfulness

Pregnancy and breastfeeding OPDIVO may harm your unborn baby

about birth control methods that you can use during this time.

The treating doctor will perform blood tests to monitor side effects

Women who are able to become pregnant: blood in vour urine The treating doctor should perform a pregnancy test before you start receiving
 swelling of your ankles This medicine has been prescribed for the treatment of your ailment. Do not

• You should use an effective method of birth control during treatment and for

Skin problems.

> skin blistering or skin peeling with OPDIVO swollen lymph nodes freed during treatment with OPDIVO and for 5 months after taking
>
> • fever or flu-like symptoms

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

Tests and follow up:

(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 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

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.

· itching or rash • OPDIVO is administered by healthcare professionals directly into the vein through an intravenous (IV) line over 60 minutes or 30 minutes, depending on shortness of breath or wheezing the dosage and frequency determined by the doctor. • When OPDIVO is used alone, it is usually given every 2 weeks or every 4 feel like passing out

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 (allogeneic). 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 • 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 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

• 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 n 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-bas 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 esophagea

squamous cell carcinoma, 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 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 complete resection of esophageal cancer or gastroesophageal junction consists with residual pathological disease in adults treated with ines in the dark! Check the label and dose every time you OPDIVO, in combination with fluoropyrimidine and platinum-based take a medicine. Wear glasses if you need them.

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 recurrent or metastatic esophageal squamous cell carcinoma after prior 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.

lead to death. These problems may appear at any time during treatment or chemotherapy is indicated for treatment of adults with unresectable, advanced even after treatment has ended. You may experience more than one of these Some of these problems may happen more often when OPDIVO is used in

These problems may sometimes become serious or life-threatening and may

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.

· 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

Liver problems severe nausea or vomiting

 dark urine (tea colored) Hormone glands problems. headaches that will not go away or unusual headaches · eye sensitivity to light

• severe stomach-area (abdominal) pain or tenderness

• nerve inflammation (neuritis) rapid heartbeat paralysis of the fibular nerve in the leg characterized by pain in the calf,
 hair loss decreased sensation or numbness, muscle weakness, and in severe cases • decreased appetite increased sweating extreme tiredness foot drop or typical limping (peroneal nerve palsy) weight gain or weight loss feeling more thirsty or hungry than usual muscles pain, muscles weakness not due to exercise (myopathy)

urinating more often than usual

· decrease in your amount of urine

painful sores or ulcers in mouth or nose, throat, or genital area

• chest pain, irregular heartbeat, shortness of breath or swelling of ankles

neck, balance problems, tingling or numbness of the arms or legs

severe or persistent muscle pain or weakness, muscle cramps

symptoms listed below when receiving the OPDIVO infusion:

or worsening signs or symptoms, which may include:

low red blood cells count, predisposition to bruising

type of organ transplant that you have had.

from becoming more serious.

stop treatment with OPDIVO.

chills or shaking

vomiting

chills

· death due to side effects

Severe infusion-related side effects

hair loss

· feeling cold

Kidney problems

loss of appetite

· Sjogren's syndrome, a disease in which the immune system attacks mainly headache lacrimal and salivary glands dizziness · chronic joints inflammation usually involving the spinal joints · abnormal laboratory test results spondyloarthropathy) Uncommon side effects, affect 1-10 patients in 1,000 users: pneumonia low blood pressure • adrenal glands insufficiency (decrease in the level of hormones secreted by adrenal glands located above the kidneys)

muscles inflammation (myositis

 sudden death gastrointestinal bleeding septic shock • esophageal fistula Side effects occurring when OPDIVO is administered in combination with ipilimumab include cabozantinib include: Very common side effects, affect more than 1 in 10 user

 feeling tired fever swelling (edema) Problems may also happen in other organs and tissues. These are not • itching, widespread itching all of the signs and symptoms of immune system problems that may diarrhea nappen with OPDIVO. Contact the treating doctor right away for any new nausea vomiting

• confusion, sleepiness, memory problems, changes in mood or behavior, stiff • stomach-area (abdominal) pain swollen stomach (abdomen) due to fluid accumulation (ascites double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight dry mouth dyspepsia · difficulty swallowing Rejection of a transplanted organ or tissue. Your doctor will tell you what · ulcers or sores in the mouth (stomatitis) signs and symptoms you should report and will monitor you depending on the inflammation of the colon (colitis) pain in muscles, bones, and joints Getting medical treatment right away may help prevent these problems • cough, cough with phlegm shortness of breath, shortness of breath upon exertion cough

The treating doctor will check you for these problems during treatment with pneumonia OPDIVO. The doctor may treat you with corticosteroids or hormone replacement

• upper respiratory tract infection medicines. If the side effects are severe, the doctor may delay or completely inflammation of the lung tissues (pneumonitis) characterized by coughing and difficulty breathing, shortness of breath and cough decreased appetite Tell your treating doctor or nurse immediately if you experience any of the • headache

 dizziness • flu-like illness • weakness, generally feeling unwell low blood pressure • low thyroid hormone levels [hypothyroidism (decreased activity of the thyroid Uncommon side effects, affect 1-10 in 1,000 users:

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

feeling tired

vomiting

rash

stomach-area (abdominal) pain

• swelling (edema)

generally feeling unwell

gland)] that can cause fatigue and weight gain high thyroid hormone levels [hyperthyroidism (increased activity of the thyroid · back or neck pain gland)] that can cause rapid heart rate, sweating and weigh loss Complications of stem cell transplantation using donor stem cells adrenal glands insufficiency (decrease in the level of hormones secreted by These complications may be serious and may lead to death. These complications adrenal glands located above the kidneys) · decreased weight may happen if the transplantation was performed either before or after treatment

 difficulty sleeping with OPDIVO. Your treating doctor will monitor you for signs of complications if · abnormal laboratory test results you have undergone an allogeneic stem cell transplant Common side effects, affect 1-10 in 100 users: Additional side effects: vitiligo, a disease in which light patches appear on the skin Side effects of OPDIVO when used alone include: high blood pressure

Very common side effects, affect more than 1 in 10 users: high level of sugar in blood (hyperglycemia feeling tired intestinal perforation weakness, generally feeling unwell accumulation of fluid in the pleural cavity around the lungs (pleural effusion)
 feeling tired which may cause shortness of breath and sometimes also chest pain and • fever • swelling (edema), including swelling of the hands, ankles or feet (peripheral

 pulmonary embolism (blood clot in the lungs) inflammation of the pituitary gland (hypophysitis) dehvdration acute kidney injury • stomach-area (abdominal) pain hepatic event

 abnormal liver function · bleeding from esophageal varices difficulty swallowing death due to side effects muscle pain, muscle weakness not caused by exercise (myopathy) itching, including widespread itching • muscles inflammation (myositis) vitiligo, a disease in which light patches appear on the skin nerve inflammation (neuritis)

 ervthema manifested by skin redness and inflammation paralysis of the fibular nerve in the leg characterized by pain in the calf,
 abnormal laboratory test results pain in muscles, bones, and joints decreased sensation or numbness, muscle weakness, and in severe cases headache foot drop or typical limping (peroneal nerve palsy) dizziness Sjogren's syndrome, a disease in which the immune system attacks mainly · upper respiratory tract infection

lacrimal and salivary glands nasal congestion chronic joints inflammation usually involving the spinal joints pneumonia, including pneumonia involving the bronchi (spondyloarthropathy)

 cough, cough with phlegm • numbness, pain, tingling or burning in the hands or feet (peripheral · shortness of breath, shortness of breath upon exertion · decreased appetit infusion-related reactions decreased weight Uncommon side effects, affect 1-10 in 1,000 users: back pain

 inflammation of the brain (encephalitis) low thyroid hormone levels [hypothyroidism (decreased activity of the thyroid · muscle inflammation leading to necrosis gland)] that can cause fatigue and weight gain eye pain and redness - inflammation of the uvea (uveitis) nigh thyroid hormone levels [hyperthyroidism (increased activity of the thyro gland)] that can cause rapid heart rate, sweating and weight loss platinum-containing chemotherapy and another chemotherapy medicine 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) • nausea constipation infusion-related reactions vomiting diarrhea Common side effects, affect 1-10 in 100 users:

 abdominal pair irregular heartbeat inflammation of the eye iris and ciliary body (iridocyclitis) · decreased appetite • inflammation of the nerves manifested by numbness, weakness, tingling, or • rash pain accompanied by burning sensation (sensory and peripheral neuropathy) • itching intestinal perforation

• numbness, pain, tingling or burning in the hands or feet (peripheral neuropathy) ulcers or sores in the mouth (stomatitis) • severe skin condition that causes red, sometimes itchy spots, similar to the headache rash of measles, which starts on the limbs and sometimes on the face and the • pain in muscles, bones and joints rest of the body (erythema multiforme) urinary tract infection • low thyroid hormone levels [hypothyroidism (decreased activity of the thyroid severe inflammation of the skin manifested by redness and peeling of gland)] that can cause fatigue and weight gain

extensive skin areas (exfoliative dermatitis) abnormal kidney function • accumulation of fluid in the pleural cavity around the lungs (pleural effusion) • blood in urine which may cause shortness of breath and sometimes also chest pain and • weight loss · abnormal laboratory test results

 pulmonary embolism (blood clot in the lungs) Common side effects, affect 1-10 in 100 users: • inflammation of the lung tissues (pneumonitis) characterized by coughing and • pneumonia difficulty breathing, shortness of breath and cough severe allergic reaction (anaphylactic reaction) • interstitial lung disease characterized by shortness of breath and dry cough, • acute kidney injury and causing lung scarring

• respiratory failure (extreme difficulty breathing) pulmonary embolish acute renal injury Side effects occurring when OPDIVO is administered in combination with pilimumab, platinum-containing chemotherapy and another chemotherapy • general health condition deterioration medicine include: intestinal obstruction (small intestine obstruction)

Very common side effects, affect more than 1 in 10 users: • inflammation of the colon (colitis) feeling tired liver problems • pain in muscles, bones, and joints • swollen stomach (abdomen) due to fluid accumulation (ascites) nausea bleeding from esophageal varices diarrhea dry mouth constipation flu-like illness

· itching, including widespread itching

gland)] that can cause fatigue and weight gain

cough

shortness of breath

In addition to the active ingredient, the medicine also contains: Mannitol, sodium citrate dihydrate, sodium chloride, polysorbate 80, pentetic acid • low thyroid hormone levels [hypothyroidism (decreased activity of the thyroid a few particles OPDIVO is available in a 10 ml (100 mg) single-use vial and a 4 ml (40 mg)

and water for injection. May contain hydrochloric acid and/or sodium hydroxide

What the medicine looks like and the contents of the package: A clear to opalescent, colorless to slightly yellowish liquid. The liquid may contain

Ministry of Health:

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Manufacturer's name and address: Bristol-Myers Squibb Holdings Pharma Ltd., Common side effects, affect 1-10 in 100 users: Liability Company, Manati, Puerto Rico, USA Registration holder's name and address: Bristol-Myers Squibb (Israel) Ltd... • fever due to low level of neutrophils, a type of white blood cell (febrile 18 Aharon Bart St. P.O. Box. 3361, Kiryat Arye, Petach Tikva 4951448 Registration number of the medicine in the National Drug Registry of the

neutropenia) • inflammation of the lung tissues (pneumonitis) characterized by coughing and difficulty breathing, shortness of breath and cough • respiratory failure (extreme difficulty breathing) · death due to side effect Side effects occurring when OPDIVO is administered in combination with

Very common side effects, affect more than 1 in 10 users diarrhea • stomach-area (abdominal) pair vomiting dvspepsia · feeling tired or weak

• liver problems. See "Liver problems" in section "Severe side effects related to immune system activity" liver toxicity • rash, redness, pain, swelling or blistering of the hands or feet · sores or ulcers in the mouth (stomatitis

 high blood pressure • low thyroid hormone levels [hypothyroidism (decreased activity of the thyroid gland)] that can cause fatigue and weight gain · decreased appetite · change in the sense of taste headache

· voice disorders (difficulty speaking due to disorders of the pharynx, vocal cords, tongue or mouth) upper respiratory tract infection abnormal laboratory test results Common side effects, affect 1-10 in 100 users:

• pulmonary embolism (blood clot in the lungs) • inflammation of the lung tissues (pneumonitis) characterized by coughing and difficulty breathing, shortness of breath and cough urinary tract infection

· death due to side effects Side effects occurring when OPDIVO is administered in combination with chemotherapy containing fluoropyrimidine and platinum include: Very common side effects, affect more than 1 in 10 users: • numbness, pain, tingling or burning in the hands or feet (peripheral neuropathy) headache

nausea diarrhea vomiting · difficulty swallowing • stomach-area (abdominal pain constipation

• ulcers or sores in the mouth (stomatitis) · swelling (edema) · decreased appetite decreased weight • pain in muscles, bones and joints

 hair loss • rash, redness, pain, swelling or blistering of the hands or feet cough, cough with phlegm

• upper respiratory tract infection · difficulty sleeping Common side effects, affect 1-10 in of 100 users

· fever due to low level of neutrophils, a type of white blood cells (febrile • inflammation of the lung tissues (pneumonitis) characterized by coughing and difficulty breathing, shortness of breath and cough • low thyroid hormone levels [hypothyroidism (decreased activity of the thyroid

gland)] that can cause fatigue and weight gain · esophageal stricture · acute kidney injury · death due to side effects For combined treatment with OPDIVO and ipilimumab, see also patient leaflet of ipilimumab

For combined treatment with OPDIVO and cabozantinib, see also patient Side effects occurring when OPDIVO is administered in combination with leaflet of cabozantinib. These are not all the possible side effects of OPDIVO. For medical information on side effects, contact your treating doctor If you experience any side effect, if any side effect gets worse, or if you

suffer from a side effect not mentioned in the leaflet, consult with the doctor Side effects can be reported to the Ministry of Health by clicking on the "Reporting side effects following drug treatment" link found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or through the following link: https://sideeffects.health.gov.il

5. HOW SHOULD THE MEDICINE BE STORED? • Avoid poisoning! This medicine, and all other medicines, must be stored in a safe place out of the reach and sight of children and/or infants, in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by a doctor! • Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month

• Storage conditions: Refrigerate at 2°C-8°C. Protect from light by storing the vial in the original package until time of use. Do not freeze or shake. • Once the infusion has been prepared: complete administration of the infusion within 7 days of preparation. In the event that the infusion is not administered immediately, OPDIVO can be stored after preparation: o at room temperature (20°C-25°C) and room light for a period of no more

than 8 hours (out of the 7 days) from the time of preparation until the end of

infusion administration.

refrigerated at a temperature of 2°C-8°C and protected from light for a period of up to 7 days from the time of preparation until the end of administration. Do not dispose of medicines via wastewater or waste bin. Ask the pharmacist. how to dispose of medicines no longer in use. These measures will help to

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6. FURTHER INFORMATION:

Preparation and Administration sually inspect for particulate matter and discoloration. OPDIVO is a clear to opalescent, colorless to pale-vellow solution. Discard if cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, • Do not freeze.

oteinaceous particles. Do not shake Administer the infusion, after dilution, over 30 minutes or 60 minutes Withdraw the required volume of OPDIVO and transfer into an intravenous depending on the dose through an intravenous line containing a sterile,

within 8 hours from the time of preparation; or

Dilute OPDIVO with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration • Administer OPDIVO in combination with other therapeutic agents as follows: ranging from 1 mg/mL to 10 mg/mL. The total volume of infusion must not

exceed 160 mL. • For adult and pediatric patients with body weight 40 kg or greater, do not exceed a total volume of infusion of 160 mL.

For adult and pediatric patients with body weight less than 40 kg,

do not exceed a total volume of infusion of 4 mL/kg of body weight. Mix diluted solution by gentle inversion. Do not shake Discard partially used vials or empty vials of OPDIVO

 The product does not contain a preservative. After preparation, store the diluted solution either:

מידע לצוות הרפואי

معلومات للطاقم الطبي

Information for Healthcare Professionals

to 1.2 micrometer)

by platinum doublet chemotherapy on the same day. With ipilimumab and platinum-doublet chemotherapy: administer OPDIVO first followed by ipilimumab and then platinum-doublet chemotherapy or the same day.

under refrigeration at 2°C to 8°C (36°F to 46°F) and protected from light for

non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micromete

With ipilimumab: administer OPDIVO first followed by ipilimumab on the

With platinum-doublet chemotherapy: administer OPDIVO first followed

diluted solution if not used within 7 days from the time of preparation.

no more than 7 days from the time of preparation to end of infusion. Discard

With fluoropyrimidine- and platinum-containing chemotherapy: administe OPDIVO first followed by fluoropyrimidine- and platinum-containing

chemotherapy on the same day Use separate infusion bags and filters for each infusion • at room temperature and room light for no more than 8 hours from the time Flush the intravenous line at end of infusion.

of preparation to end of the infusion. Discard diluted solution if not used • Do not co-administer other drugs through the same intravenous line