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.

Pocket guide and patient safety information card
In addition to the leaflet, 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 pocket guide, the 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 with advanced (unresectable or metastatic) melanoma.
  - OPDIVO is indicated as complementary (adjuvant) treatment for patients with melanoma involving the lymph nodes or metastatic melanoma after complete resection.

- **Metastatic 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 adult patients 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 patients 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 patients with advanced renal cell carcinoma at moderate or high risk.
  - OPDIVO in combination with cabozantinib is indicated as first-line treatment for patients with advanced renal cell carcinoma.
  - OPDIVO used alone is indicated for the treatment of patients 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 patients 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 patients with urinary tract or bladder cancer at high risk of disease recurrence after radical tumor resection.
  - OPDIVO is indicated for treatment of patients 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 (neo-adjuvant) 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 adult and pediatric patients 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 used alone or in combination with ipilimumab, is indicated for patients with liver cancer with mild liver impairment (Child-Pugh A) following treatment with sorafenib.

- **Esophageal cancer**
  - OPDIVO is indicated as complementary (adjuvant) treatment after complete resection of esophageal cancer or gastroesophageal junction cancer with residual pathological disease in patients treated with chemoradiation therapy prior to resection.
  - OPDIVO is indicated for treatment of patients 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 patients 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
- 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 metastatic colorectal cancer expressing dMMR or MSI-H, or
- in children below the age of 18 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 at least 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 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 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 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 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 <u>every time</u> 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. <u>SIDE EFFECTS</u>

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 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.
- onset of cough or worsening 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
- eye problems

- rapid heart beat
- 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
- painful sores or ulcers in mouth or nose, throat, or genital area

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

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
- fever
- back or neck pain

Complications of stem cell transplantation using donor stem cells (allogeneic).
These complications may be severe 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 include:

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
- stomach-area (abdominal) pain
- constipation
- swollen stomach
- dyspepsia
- difficulty swallowing
- rash
- itchy skin, including widespread itching
- vitiligo, 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)
- liver problems
- dry skin
- swollen stomach (abdomen) due to fluid accumulation (ascites)
- bleeding from esophageal varices
- dry mouth
- flu-like illness
- flu
- chills
- death due to side effects
- 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
- muscles pain, muscles weakness not due to exercise (myopathy)
- 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 (spondyloarthropathy)

Uncommon side effects, affect 1-10 patients in 1000 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
- septic shock
- esophageal fistula

<u>Side effects occurring when OPDIVO is administered in combination with ipilimumab include:</u>

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
- stomach-area (abdominal) pain
- constipation
- swollen stomach (abdomen) due to fluid accumulation (ascites)
- dry mouth
- dyspepsia
- ulcers or sores in the mouth (stomatitis)
- inflammation of the colon (colitis)
- pain in muscles, bones, and joints
- cough, cough with phlegm
- shortness of breath, shortness of breath upon exertion
- pneumonia
- upper respiratory tract infection
- inflammation of the lung tissues (pneumonitis) characterized by coughing and difficulty breathing, shortness of breath and cough
- decreased appetite
- headache
- dizziness
- flu
- flu-like illness
- weakness, generally feeling unwell
- chills
- low blood pressure
- 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 weigh loss
- adrenal glands insufficiency (decrease in the level of hormones secreted by adrenal glands located above the kidneys)
- decreased weight
- difficulty sleeping
- abnormal laboratory test results

Common side effects, affect 1-10 in 100 users:
- vitiligo, a disease in which light patches appear on the skin
- high blood pressure
- high level of sugar in blood (hyperglycemia)
- intestinal perforation
- 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 pituitary gland (hypophysitis)
- swollen stomach
- dehydration
- acute kidney injury
- hepatic event
- bleeding from esophageal varices
- death due to side effects
- muscle pain, muscle weakness not caused by exercise (myopathy)
- muscles inflammation (myositis)
- 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)
- Sjogren's syndrome, a disease in which the immune system attacks mainly lacrimal and salivary glands
- chronic joints inflammation usually involving the spinal joints (spondyloarthropathy)
- infusion-related reactions

Uncommon side effects, affect 1-10 in 1000 users:
- inflammation of the brain (encephalitis)
- muscle inflammation leading to necrosis
- eye pain and redness - inflammation of the uvea (uveitis)

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

Very common side effects, affect more than 1 in 10 users
- feeling tired
- fever
- pain in muscles, bones, and joints
- nausea
- diarrhea
- constipation
- vomiting
- stomach-area (abdominal) pain
- rash
- itching, including widespread itching
- hair loss
- decreased appetite
- cough
- shortness of breath
- low thyroid hormone levels [hypothyroidism (decreased activity of the thyroid gland)] that can cause fatigue and weight gain
- headache
- dizziness
- abnormal laboratory test results

Common side effects, affect 1-10 in 100 users:
- pneumonia
- fever due to low level of neutrophils, a type of white blood cell (febrile neutropenia)
- acute kidney injury
- 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 effects

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

Very common side effects, affect more than 1 in 10 users:
- diarrhea
- nausea
- stomach-area (abdominal) pain
- vomiting
- dyspepsia
- 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)
- rash
- itching
- high blood pressure
- low thyroid hormone levels [hypothyroidism (decreased activity of the thyroid gland)] that can cause fatigue and weight gain
- pain in muscles, bones and joins
- decreased appetite
- change in the sense of taste
- headache
- cough
- 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:
- pneumonia
- 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

Uncommon side effects, affect 1-10 in 1000 users:
- 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
- stomach-area (abdominal pain)
- constipation
- ulcers or sores in the mouth (stomatitis)
- feeling tired
- fever
- swelling (edema)
- decreased appetite
- decreased weight
- pain in muscles, bones and joints
- rash
- rash, redness, pain, swelling or blistering of the hands or feet
- cough
- upper respiratory tract infection

Common side effects, affect 1-10 in of 100 users:
- pneumonia
- fever due to low level of neutrophils, a type of white blood cells (febrile neutropenia)
- inflammation of the lung tissues (pneumonitis) characterized by coughing and difficulty breathing, shortness of breath and cough

For combined treatment with OPDIVO and ipilimumab, see also patient leaflet of ipilimumab.
For combined treatment with OPDIVO and cabozantinib, see also patient 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 2ºC-8ºC. 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 24 hours of preparation. In the event that the infusion is not administered immediately, OPDIVO can be stored:
  - at room temperature (20ºC-25ºC) and room light for a period of no more than 8 hours (out of the 24 hours) from the time of preparation until the end of infusion administration.
    or

- refrigerated at a temperature of 2ºC-8ºC and protected from light for a period of up to 24 hours 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 protect the environment.

6. FURTHER INFORMATION:

In addition to the active ingredient, the medicine also contains:
Mannitol, sodium citrate dihydrate, sodium chloride, polysorbate 80, pentetic acid 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 a few particles. OPDIVO is available in a 10 ml (100 mg) single-use vial and a 4 ml (40 mg) single-use vial.

Manufacturer's name and address: Bristol-Myers Squibb Holdings Pharma Ltd., Liability Company, Manati, Puerto Rico, USA.

Registration holder's name and address: Bristol-Myers Squibb (Israel) Ltd., 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 Ministry of Health:
153-55-34333-00

Revised in July 2022 according to MOH guidelines.

מידע לצוות הרפואי

معلومات للطاقم الطبي

Information for healthcare professionals

Preparation and Administration

Visually inspect for particulate matter and discoloration. OPDIVO is a clear to opalescent, colorless to pale-yellow solution. Discard if cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake.

Preparation

- Withdraw the required volume of OPDIVO and transfer into an intravenous container.
- Dilute OPDIVO with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration 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:
    - at room temperature and room light for no more than 8 hours from the time of preparation to end of the infusion. Discard diluted solution if not used within 8 hours from the time of preparation; or
    - under refrigeration at 2°C to 8°C (36°F to 46°F) and protected from light for no more than 24 hours from the time of preparation to end of infusion. Discard diluted solution if not used within 24 hours from the time of preparation.
- Do not freeze.

Administration

- Administer the infusion, after dilution, over 30 minutes or 60 minutes depending on the dose through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).
- Administer OPDIVO in combination with other therapeutic agents as follows:
    - With ipilimumab: administer OPDIVO first followed by ipilimumab on the same day.
    - With platinum-doublet chemotherapy: administer OPDIVO first followed 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 on the same day.
    - With fluoropyrimidine- and platinum-containing chemotherapy: administer OPDIVO first followed by fluoropyrimidine- and platinum-containing chemotherapy on the same day.
- Use separate infusion bags and filters for each infusion.
- Flush the intravenous line at end of infusion.
- Do not co-administer other drugs through the same intravenous line.