Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986
This medicine is dispensed with a doctor's prescription only

Opdualag®

Concentrate for solution for infusion

Active ingredients and their concentrations:
nivolumab 12 mg/ml
relatlimab 4 mg/ml

One 20 ml vial of (sterile) concentrate contains 240 mg of nivolumab and 80 mg of relatlimab.

Inactive ingredients and allergens, see section 6 'Additional information'.

Read the entire leaflet carefully before you start using this medicine.
This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.
This medicine has been prescribed to treat your illness. Do not pass it on to others. It may harm them, even if it seems to you that their illness is similar to yours.

Patient card
In addition to the patient leaflet, Opdualag also has a patient card.
This card contains important safety information that you need to know and that you should follow before you start treatment and during treatment with Opdualag. Carefully read the patient card and patient leaflet before you start using the medicine. Keep the card in case you need to read it again.

1. What is this medicine intended for?

Opdualag is indicated for the treatment of adult and paediatric patients 12 years of age or older with unresectable or metastatic melanoma.

Therapeutic group: Antineoplastic agents, monoclonal antibodies

Opdualag contains two active substances: nivolumab and relatlimab. Both active substances are monoclonal antibodies, proteins designed to recognise and attach to a specific target substance in the body. Nivolumab attaches to a target protein called PD-1. Relatlimab attaches to a target protein called LAG-3.

PD-1 and LAG-3 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 the two proteins, nivolumab and relatlimab block their actions and prevent them from switching off the T cells. This helps increase the T cell activity against the melanoma cancer cells.

2. Before using this medicine

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredients (nivolumab, relatlimab) or to any of the other ingredients in this medicine (see section 6). Contact your doctor if you are not sure.

Special warnings about using this medicine
Before treatment with Opdualag, talk to your doctor as the medicine may cause:
- 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 inflammation of the intestines (colitis) with symptoms 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 test results, eye or skin yellowing (jaundice), pain in the right side of your stomach area or tiredness.
- Inflammation of or problems with your kidneys. Signs and symptoms may include abnormal kidney function test results or decrease in the amount of urine.
- Problems with your hormone producing glands (including the pituitary, thyroid and adrenal glands), which may affect how these glands work. Signs and symptoms indicating that these glands are not working properly may include fatigue (extreme tiredness), weight change, or headache 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, nausea or vomiting, stomach pain and deep or fast breathing.
- Inflammation of the skin that can lead to severe skin reaction (known as toxic epidermal necrolysis [TEN] 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 heart muscle (myocarditis). Signs and symptoms may include chest pain, irregular and/or rapid heartbeat, fatigue, swelling of the ankles or shortness of breath.
- Haemophagocytic lymphohistiocytosis (HLH). A rare disease in which your immune system makes too many normal immune system cells (infection-fighting) called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, swollen lymph glands, breathing problems, easy bruising, kidney abnormalities and heart problems.
- Organ transplant rejection.
- Graft-versus-host disease after stem cell transplantation (where the transplanted cells from a donor attack your own cells). If you have received one of these transplants, your doctor will consider whether you should receive treatment with Opdualag. Graft-versus-host disease can be severe and can lead to death.
- Infusion reactions, which may include shortness of breath, itching or rash, dizziness or fever.

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 use on your own. Your doctor may:
- give you other medicines to prevent complications and reduce your symptoms,
- skip your next dose of Opdualag,
- or stop your treatment with Opdualag altogether.

Please note that these signs and symptoms are sometimes delayed and may develop weeks or months after your last dose.

Tests and follow-up
Before treatment, your doctor will check your general health. You will also have blood tests during the treatment.

Before you receive Opdualag, check with your doctor if:
- you have an active autoimmune disease (a disorder where the body attacks its own cells);
- you have melanoma of the eye;
- you have been told that your cancer has spread to your brain;
- you have been taking medicines for immune system suppression.

Children and adolescents
Opdualag is not intended for use in children below 12 years of age. There is no information regarding the efficacy and safety of using Opdualag in children below 12 years of age.

Drug interactions
Tell the doctor or pharmacist if you are taking, have recently taken or are planning to take other medicines, including non-prescription medicines and dietary supplements. Do not take any other medicines during the treatment without talking to your doctor first.
Before you receive Opdualag, tell your doctor if you are taking any medicines that suppress the immune system, such as corticosteroids, since these medicines may interfere with the effect of Opdualag. However, once you are treated with Opdualag, your doctor may give you corticosteroids to reduce any possible side effects that you may have during the treatment.

Pregnancy, breastfeeding and fertility
If you are pregnant or breastfeeding, think you may be pregnant or are planning to become pregnant, ask your doctor for advice before taking this medicine.

Pregnancy
Do not use Opdualag if you are pregnant, unless your doctor specifically tells you to. The effects of Opdualag on pregnant women are not known, but it is possible that the active substances, nivolumab and relatlimab, could harm the foetus.
- If you are a woman who could become pregnant, you must use effective contraception while you are being treated with Opdualag and for at least 5 months following the last dose of Opdualag.
- If you become pregnant while using Opdualag, tell your doctor.

Breastfeeding
It is not known whether Opdualag can pass into breast milk and affect a baby that is breast-fed. Talk to your doctor about the benefits and risks before breastfeeding during or after treatment with Opdualag.

Driving and using machines
Opdualag has a minor influence on the ability to drive and use machines; however, use caution when performing these activities until you are sure that Opdualag does not adversely affect you, in view of possible side effects, such as fatigue and dizziness (see section 4).
Regarding children over 12 years of age, they should be warned against riding a bicycle or playing near the road, etc.

3. How to use this medicine?

Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dosage or about how to take this medicine. Only your doctor will determine your dosage and how you should take this medicine.
The recommended dosage by infusion for adults and children 12 years of age and older is 480 mg nivolumab and 160 mg relatlimab every 4 weeks. This dosage has been established for children aged 12 years and older weighing at least 30 kg.

Do not exceed the recommended dose.

Method of administration
Opdualag may be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection before use. Opdualag may also be used undiluted.

Treatment with Opdualag is given in a hospital or clinic, under the supervision of an experienced doctor.

Opdualag is given as an infusion into a vein, every 4 weeks. Each infusion administration takes about 30 minutes.

Treatment duration
Your doctor will continue treating you with Opdualag for as long as you keep benefitting from it or until you develop side effects which are too severe.

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

If you miss a dose of Opdualag
It is very important for you to keep all your appointments to receive Opdualag. If you miss an appointment, ask your doctor when to schedule an appointment for the next dose administration.
Adhere to the treatment as recommended by your doctor.

If you stop using Opdualag
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with Opdualag, unless you have discussed this with your doctor.

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 any further questions about using this medicine, consult your doctor or pharmacist.

4. Side effects

Like with all medicines, using Opdualag may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them. Your doctor will discuss them with you and will explain the risks and benefits of the treatment.

You must be aware of important symptoms of inflammation (described in section 2 under 'Special warnings about using this medicine'). Opdualag acts on the immune system and may cause inflammation in various areas of the body. Inflammation may cause serious damage to your body, and some inflammatory conditions may be life-threatening and need treatment or discontinuation of Opdualag treatment.

The following side effects have been reported with the use of Opdualag:

Very common side effects, affect more than 1 in 10 users:
- infection of the urinary tract (the parts of the body that collect and pass out urine)
- decreased number of red blood cells (which carry oxygen) and white blood cells (lymphocytes, neutrophils, leucocytes, which are important in fighting infection)
- underactive thyroid gland (which can cause tiredness or weight gain)
- decreased appetite
- headache
- difficulty breathing; cough
- diarrhoea (watery, loose or soft stools); vomiting; nausea; stomach pain; constipation
- skin rash (sometimes with blisters); vitiligo, appearance of light patches on the skin; itching
- pain in the muscles, bones and joints
- feeling tired or weak; fever

Changes in the results of tests carried out by your doctor may show:
- abnormal liver function (increased levels of the liver enzymes alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase in your blood)
- abnormal kidney function (increased levels of creatinine in your blood)
- decrease of sodium and magnesium levels, and decrease or increase of calcium and potassium levels

Common side effects, affect 1-10 in 100 users:
- infections of the upper respiratory tract (nose and upper airways)
- decreased number of platelets (cells which help the blood to clot); increase in some white blood cells
- decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys); inflammation of the pituitary gland situated at the base of the brain; overactive thyroid gland; inflammation of the thyroid gland
- diabetes; low sugar levels in the blood; weight loss; high levels of the waste product uric acid in the blood; decreased levels of the protein albumin in the blood; dehydration
- state of confusion
- inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs); dizziness; changes in the sense of taste
- inflammation of the eye (which causes pain and redness, vision problems or blurry vision); vision problems; dry eyes; excessive tear production
- inflammation of the heart muscle
- inflammation of a vein, which can cause redness, tenderness and swelling
- inflammation of the lungs (pneumonitis), characterised by coughing and difficulty breathing; nasal congestion (blocked nose)
- inflammation of the colon (colitis); inflammation of the pancreas; inflammation of the stomach (gastritis); difficulty swallowing; mouth ulcers and cold sores (stomatitis); dry mouth
- inflammation of the liver (hepatitis)
- unusual hair loss or thinning (alopecia); isolated area of skin growth that becomes red and itchy (lichenoid keratosis); sensitivity to light; dry skin
- painful joints (arthritis); muscle spasms; muscle weakness
- kidney failure (changes in amount or colour of urine, blood in urine, swelling of the ankles, loss of appetite); high levels of proteins in the urine
- oedema (swelling); flu-like symptoms; chills
- reactions related to the administration of the medicine.

Changes in the results of tests carried out by your doctor may show:
- abnormal liver function (higher blood levels of the waste product bilirubin, higher blood levels of the liver enzyme gamma-glutamyl transferase)
- increase in sodium and magnesium levels
- increased level of troponin (a protein released into the blood when the heart is damaged)
- increased levels of the enzyme that breaks down glucose (sugar) (lactate dehydrogenase), the enzyme that breaks down fats (lipase), the enzyme that breaks down starch (amylase).

Uncommon side effects, affect 1-10 in 1,000 users:
- inflammation and infection in the hair follicles
- disorder in which red blood cells are destroyed at a rate faster than their production rate (haemolytic anaemia)
- underactive function of the pituitary gland situated at the base of the brain; underactive function of the glands producing sex hormones
- inflammation of the brain, which may include confusion, fever, memory problems or seizures (encephalitis); a temporary inflammation of the nerves that causes pain, weakness, and paralysis in the extremities (Guillain-Barré syndrome); inflammation of the optic nerve that may cause a complete or partial loss of vision
- an inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada disease); red eyes
- accumulation of fluid around the heart
- asthma
- inflammation of the oesophagus (passage between throat and stomach)
- inflammation of the bile duct
- skin rash and blistering on the legs, arms, and abdomen (pemphigoid); skin disease with thickened patches of red skin, often with silvery scales (psoriasis); hives (itchy, bumpy rash)
- inflammation of the muscles causing weakness, swelling, and pain; disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome); inflammation of the muscles causing pain or stiffness; inflammation of the joints (painful joint disease); disease in which the immune system attacks its own tissues, causing widespread inflammation and tissue damage in the affected organs, such as joints, skin, brain, lungs, kidneys, and blood vessels (systemic lupus erythematosus)
- inflammation of the kidney
- absence of sperm in the semen
- fluid around the lungs.

Changes in the results of tests carried out by your doctor may show:
- increase in level of c-reactive protein (CRP)
- red blood cell sedimentation rate increased.

Rare side effects, affect 1-10 in 10,000 users:
- lack or reduction of digestive enzymes made by the pancreas (pancreatic exocrine insufficiency)
- inflammation of the tissues lining the lungs (pleura), the heart (pericardium) and the abdomen (peritoneum).

Side effects of unknown frequency (the frequency of these effects has not been established yet):
- coeliac disease (characterized by symptoms such as stomach pain, diarrhoea, and bloating after consuming gluten-containing foods).

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.
You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: https://sideeffects.health.gov.il

5. How to store the medicine?

- Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- Do not use the medicine after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.

Storage conditions
Opdualag is given in a hospital or clinic and the healthcare professionals are responsible for its storage.
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
The unopened vial can be stored at controlled room temperature (up to 25°C) for up to 72 hours.

6. Additional information

In addition to the active ingredients, this medicine also contains:
Sucrose, histidine hydrochloride monohydrate, histidine, polysorbate 80, pentetic acid, and water for injection

What the medicine looks like and contents of the pack:
A clear to opalescent, colourless to slightly yellow liquid that is essentially free of particles.
The medicine is available in packs containing one glass vial containing 20 ml of solution.

Registration holder's name and address:
Bristol-Myers Squibb (Israel) Ltd., 18 Aharon Bart St. P.O. Box 3361, Kiryat Arye, Petach Tikva 4951448.

Manufacturer's name and address:
Bristol-Myers Squibb Company, Route 206 & Province Line Road, Princeton, New Jersey 08543, USA

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 171-74-37423-00

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מידע לצוות הרפואי

معلومات للطاقم الطبي

Information for Healthcare Professionals

Opdualag is supplied as a single-dose vial and does not contain any preservatives. Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.
Opdualag can be used for intravenous administration either:

- without dilution, after transfer to an infusion container using an appropriate sterile syringe;
  or
- after diluting according to the following instructions:
  - the final infusion concentration should range between 3 mg/mL nivolumab and 1 mg/mL relatlimab to 12 mg/mL nivolumab and 4 mg/mL relatlimab.
  - the total volume of infusion must not exceed 160 mL. For patients weighing less than 40 kg, the total volume of infusion should not exceed 4 mL per kilogram of patient weight.

Opdualag concentrate may be diluted with either:

- sodium chloride 9 mg/mL (0.9%) solution for injection; or
- 50 mg/mL (5%) glucose solution for injection.

Preparing the infusion

- Inspect the Opdualag concentrate for particulate matter or discolouration. Do not shake the vial. Opdualag is a clear to opalescent, colourless to slightly yellow solution. Discard the vial if the solution is cloudy, discoloured, or contains extraneous particulate matter.
- Withdraw the required volume of Opdualag concentrate using an appropriate sterile syringe and transfer the concentrate into a sterile, intravenous container (ethylvinyl acetate (EVA), polyvinyl chloride (PVC), or polyolefin). Each vial is filled with 21.3 mL of solution, which includes an overfill of 1.3 mL.
- If applicable, dilute Opdualag solution with the required volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. For ease of preparation, the concentrate can also be transferred directly into a pre-filled bag containing the appropriate volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.
- Gently mix the infusion by manual rotation. Do not shake.

Administration

Opdualag infusion must not be administered as an intravenous push or bolus injection.

Administer the Opdualag infusion intravenously over a period of 30 minutes.
Use of an infusion set and an in-line or add-on filter, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm) is recommended.

Opdualag infusion is compatible with EVA, PVC and polyolefin containers, PVC infusion sets and in-line filters with polyethersulfone (PES), nylon, and polyvinylidene fluoride (PVDF) membranes with pore sizes of 0.2 µm to 1.2 µm.

Do not co-administer other medicinal products through the same infusion line.
After administration of the Opdualag dose, flush the line with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.

Storage conditions and shelf life

Unopened vial

Opdualag 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. Opdualag should not be frozen.
The unopened vial can be stored at controlled room temperature (up to 25°C) for up to 72 hours.

Do not use Opdualag 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.

After preparation of infusion

Chemical and physical in-use stability from the time of preparation has been demonstrated as follows (times are inclusive of the administration period):

Infusion preparation	**Chemical and physical in-use stability**	
	Storage at 2°C to 8°C protected from light	**Storage at room temperature (≤ 25°C) and room light**
Undiluted or diluted with sodium chloride 9 mg/mL (0.9%) solution for injection	30 days	24 hours (of total 30 days storage)
Diluted with 50 mg/mL (5%) glucose solution for injection	7 days	24 hours (of total 7 days storage)

From a microbiological point of view, the prepared solution for infusion, regardless of the diluent, should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless preparation has taken place in controlled and validated aseptic conditions.