

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

The medicine is dispensed with a doctor's prescription only

**YERVOY 5 mg/ml
Concentrate for solution for intravenous infusion**

Active ingredient and concentration:

ipilimumab 5 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 'Additional 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 YERVOY in combined treatment with nivolumab, carefully read the patient leaflet that comes with nivolumab 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 to yours.

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

Patient pocket guide and safety information card

In addition to the leaflet, YERVOY has a patient pocket guide and safety information card.

The pocket guide and card contain important safety information, which you have to know before starting and during the treatment with YERVOY and which you must follow. Read the pocket guide, card and patient leaflet before you start using this medicine. Keep the card and pocket guide for further reference if needed.

1. WHAT IS THIS MEDICINE INTENDED FOR?

1. Unresectable or metastatic skin cancer called melanoma

YERVOY used alone or in combination with nivolumab is intended for the treatment of advanced (unresectable or metastatic) melanoma.

2. Advanced renal cell carcinoma

YERVOY in combination with nivolumab is intended as first-line treatment for patients with advanced renal cell carcinoma at moderate or high risk.

3. Metastatic colon or rectal cancer (colorectal cancer)

YERVOY in combination with nivolumab is intended as treatment of adults and children 12 years of age and older with metastatic colon or rectal cancer that expresses dMMR (mismatch repair deficient) or MSI-H (microsatellite instability-high) whose disease has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

4. Metastatic non-small cell lung cancer

YERVOY in combination with nivolumab and 2 treatment cycles of combined platinum-containing chemotherapy (platinum-doublet chemotherapy), intended as first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer and with no changes in the EGFR or ALK genes in the tumor.

5. **Liver cancer (hepatocellular carcinoma)**

YERVOY in combination with nivolumab is intended as treatment for liver cancer with mild liver impairment (Child-Pugh A) in patients who were previously treated with sorafenib.

6. **Malignant pleural mesothelioma** – cancer of the mesothelial cells comprising the pleura (lining of the lungs).

YERVOY in combination with nivolumab is intended as first-line treatment for adults with unresectable malignant pleural mesothelioma.

7. **Esophageal squamous cell carcinoma**

YERVOY in combination with nivolumab 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 $\geq 1\%$ of the tumor cells.

Therapeutic group: antineoplastic.

2. BEFORE USING THE MEDICINE:

Do not use this medicine if:

- | |
|---|
| <ul style="list-style-type: none">• you are sensitive (allergic) to the active ingredient (ipilimumab) or to any of the other ingredients in this medicine (see section 6). |
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Special warnings regarding use of this medicine:

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

- you have immune system problems such as ulcerative colitis, Crohn's disease, or lupus
- you have received an organ transplant
- you have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic transplant)
- 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 'Pregnancy and breastfeeding' section
- you are breastfeeding or planning to breastfeed - see the 'Pregnancy and breastfeeding' section

Children and adolescents:

YERVOY is intended for children and adolescents over the age of 12 for MSI-H or dMMR metastatic colon or rectal cancer, as the safety and efficacy of use have been proven for these indications.

Tests and follow up:

The treating doctor will perform blood tests before and during treatment with YERVOY.

Drug interactions:

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

Pregnancy and breastfeeding:

YERVOY may harm your unborn baby.

Women who are able to become pregnant:

- The treating doctor will perform a pregnancy test before starting treatment with YERVOY.
- You must use effective contraception during treatment and for at least 3 months after administration of your last dose of YERVOY. Speak to the doctor about the methods of contraception you can use during this time.
- If you become pregnant or think you are pregnant during treatment with YERVOY, inform the treating doctor immediately.

Breastfeeding:

- Inform the treating doctor if you are breastfeeding or planning to breastfeed. It is not known if YERVOY can pass into breast milk.
- Do not breastfeed during treatment with YERVOY and for 3 months after your last dose of YERVOY.

Driving and operating machinery:

Do not drive, pedal or operate machines after receiving YERVOY, unless you are sure that you feel well. Feeling tired or weak is a very common side effect of YERVOY. It may affect your ability to drive, pedal or operate machines.

Children should be cautioned against riding a bicycle, playing near a road, and the like.

Important information about some of this medicine's ingredients:

YERVOY contains sodium.

If you are on a low-sodium (low-salt) diet, inform the doctor prior to administration of this medicine.

The medicine contains 23 mg sodium (the main component of cooking salt/table salt) in each 10 mL vial. This amount is equivalent to 1.15% of the recommended maximum daily dietary intake of sodium for adults.

The medicine contains 92 mg sodium (the main component of cooking salt/table salt) in each 40 mL vial. This amount is equivalent to 4.60% of the recommended maximum daily dietary intake of sodium for adults.

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.

Do not exceed the recommended dose.

Treatment with YERVOY is administered by healthcare professionals.

- When YERVOY is used alone, it is administered directly into the vein through an intravenous line over 90 minutes.
- When YERVOY is used in combination with nivolumab (except for treatment of unresectable or metastatic melanoma), nivolumab is given directly into the vein through an intravenous line over 30 minutes. Then YERVOY is also given through an intravenous line over 30 minutes on the same day.
- For treatment of advanced melanoma (unresectable or metastatic), when YERVOY is used in combination with nivolumab, nivolumab is given directly into the vein through an IV line over 30 minutes. Then YERVOY is also given directly into the vein through an IV line over 90 minutes on the same day.
- YERVOY in combination with nivolumab is usually given every 3 weeks for a total of 4 treatment doses. After that, nivolumab will be given alone, usually every 2 or 4 weeks.
 - For treatment of metastatic non-small cell lung cancer that has spread to other parts of your body, YERVOY is given every 6 weeks and nivolumab is given every 3 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 that cannot be removed by surgery, YERVOY is given every 6 weeks and nivolumab is given every 2 or 3 weeks, as decided by the treating doctor. In any event, the treatment is given for up to 2 years.
 - When YERVOY is used in combination with nivolumab for treating esophageal squamous cell carcinoma, YERVOY is given every 6 weeks and nivolumab is given every 2 weeks or every 3 weeks for up to 2 years.
- The treating doctor will decide how many treatments you need.
- The treating doctor will do blood tests before starting and during treatment with YERVOY.

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

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.

Adhere to the treatment regimen as recommended by the doctor.

Do not take medicines in the dark! Check the label and dose every time you take 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 YERVOY 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.

YERVOY may cause serious side effects:

YERVOY is a medicine that may treat certain types of cancer by activating your immune system. YERVOY can 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 can sometimes become severe or life-threatening and can lead to death. You may experience more than one of these problems at the same time. These problems may appear at any stage during treatment or even after treatment has ended. Some of these problems may happen more often when YERVOY is used in combination with nivolumab.

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

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 your stomach-area (abdomen)
- dark urine (tea colored)
- bleeding or bruising more easily than normal

Skin problems.

- rash
- itching
- skin blistering or peeling
- painful sores in mouth or nose, throat, or genital area

Hormone gland problems.

- headaches that will not go away or unusual headaches
- eyes sensitivity to light
- eye problems
- rapid heartbeat
- increased sweating
- extreme tiredness
- weight gain or weight loss

- feeling more hungry or thirsty 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

Lung problems.

- new or worsening cough
- shortness of breath
- chest pain

Kidney problems.

- decrease in the amount of urine
- blood in the urine
- swelling of your ankles
- loss of appetite

Eye problems.

- blurry vision, double vision, or other vision problems
- eye pain or redness

Problems can also appear in other organs and tissues. These are not all the signs and symptoms of immune system problems that may appear with YERVOY. Contact the treating doctor right away if any new signs or symptoms appear or if signs or symptoms worsen.

- 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
- persistent or severe 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 your treatment with YERVOY. The doctor may treat you with corticosteroids or hormone replacement medicines. The treating doctor may delay or completely stop treatment with YERVOY if the side effects are severe.

Severe infusion-related reactions

Tell the treating doctor or nurse right away if you feel any of the following symptoms when receiving an infusion of YERVOY:

- chills or shaking
- itching or rash
- flushing
- shortness of breath or wheezing
- dizziness
- feel like passing out
- fever
- back or neck pain

Complications, including graft-versus-host disease (GVHD), in patients who have undergone a bone marrow (stem cell) transplant, when the source of the transplant is a donor (allogeneic transplant). These complications can be severe and can lead to death. These complications may appear if you underwent transplantation either before or after being treated with YERVOY. The treating doctor will monitor you for these complications.

Additional side effects:

Side effects during treatment with YERVOY when used alone

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

- feeling tired
- diarrhea
- nausea
- itching
- rash
- vomiting
- fever
- decreased appetite
- pain in muscles, bones and joints
- cough, cough with phlegm
- shortness of breath, shortness of breath upon exertion
- upper respiratory tract infection

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

- urticaria (hives)
- decreased weight
- inflammation of the colon (colitis)
- vitiligo – a disease in which light patches appear on the skin
- 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
- high blood pressure

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

- Colon ulcer
- esophagitis
- difficulty breathing due to fluid in the lungs (acute respiratory distress syndrome)
- renal failure
- infusion-related reaction

Side effects during combined treatment of YERVOY with nivolumab

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
- inflammation of the colon (colitis)
- swollen stomach (abdomen) due to fluid accumulation (ascites)
- dry mouth
- dyspepsia
- difficulty swallowing
- sores or ulcers in the mouth (stomatitis)
- pain in muscles, bones and joints

- cough, cough with phlegm
- shortness of breath, shortness of breath upon exertion
- inflammation of the lung tissues (pneumonitis) characterized by coughing and difficulty breathing, shortness of breath and cough
- pneumonia
- 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 weight loss
- adrenal insufficiency (decrease in the level of hormones secreted by the adrenal glands located above the kidneys)
- decreased weight
- difficulty sleeping
- upper respiratory tract infection
- abnormal laboratory test results

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

- high level of sugar in blood (hyperglycemia)
- inflammation of the pituitary gland (hypophysitis)
- dehydration
- acute kidney injury
- liver event
- abnormal liver function
- bleeding from esophageal varices
- 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)
- vitiligo – disease in which light patches appear on the skin
- high blood pressure
- intestinal perforation
- muscle pain, muscle weakness not caused by exercise (myopathy)
- Sjogren's syndrome, a disease in which the immune system primarily attacks the lacrimal and salivary glands
- chronic joint inflammation, usually involving the spinal joints (spondyloarthropathy)
- 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)
- death due to side effects
- infusion-related reactions

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

- inflammation of the brain (encephalitis)
- muscle inflammation leading to necrosis
- eye pain and redness - inflammation of the uvea (uveitis)

Side effects during combined treatment of YERVOY with nivolumab and chemotherapy

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

For combined treatment of YERVOY with nivolumab, see also the nivolumab patient leaflet.

These are not all the possible side effects of YERVOY.

For medical information regarding side effects, contact the treating doctor.

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in the leaflet, consult the 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 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:** Store under refrigeration 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.
- After preparation, the solution for infusion may be stored: under refrigeration at a temperature of 2°C-8°C, for a period of up to 24 hours from the time of preparation to the time of infusion.

6. FURTHER INFORMATION:

In addition to the active ingredient, the medicine also contains:

Mannitol; sodium chloride; tris hydrochloride; polysorbate 80; pentetic acid (DTPA); sodium hydroxide; hydrochloric acid and water for injection

What the medicine looks like and the contents of the package:

Clear to slightly opalescent and colorless to pale-yellow liquid. The liquid may contain few particulates.

YERVOY is available in a 10 ml (50 mg) single-use vial and a 40 ml (200 mg) single-use vial.

Manufacturer's name and address: Bristol-Myers Squibb, Princeton, New Jersey, 08543, 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:

147-62-33522

Revised in December 2022 according to MOH guidelines.

מידע לצוות הרפואי

معلومات للطاقم الطبي

Information for Healthcare professionals:

Preparation and Administration

- Do not shake product.
- Visually inspect for particulate matter and discoloration prior to administration. Discard vial if solution is cloudy, there is pronounced discoloration (solution may have pale-yellow color), or there is foreign particulate matter other than translucent-to-white, amorphous particles.

Preparation of Solution

- Allow the vial(s) to stand at room temperature for approximately 5 minutes prior to preparation of infusion.
- Withdraw the required volume of YERVOY and transfer into an intravenous bag.
- Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion.
- After preparation, store the diluted solution under refrigeration at 2°C to 8°C for no more than 24 hours from the time of preparation to the time of infusion.
- Discard partially used or empty vials of YERVOY.

Administration

- Do not co-administer other drugs through the same intravenous line.
- Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after each dose.
- Administer diluted solution over 30 minutes or 90 minutes depending on the dose, through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter.
- When administered in combination with nivolumab, infuse nivolumab first followed by YERVOY on the same day. When administered with nivolumab and platinum-doublet chemotherapy, infuse nivolumab first followed by YERVOY and then platinum-doublet chemotherapy on the same day. Use separate infusion bags and filters for each infusion.