

Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) – 1986

This 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

Inactive ingredients and allergens, see section 2 under 'Important information about some of this medicine's ingredients', and 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, ask the doctor or pharmacist.

If your doctor prescribed you YERVOY in combination with OPDIVO, which contains the active ingredient nivolumab, carefully read the patient leaflet that is included with OPDIVO as well.

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 safety card and information brochure

In addition to the leaflet, YERVOY has a patient safety information card. This card contains important safety information, which you should know before starting and during the treatment with YERVOY and which you should follow. Read the card and patient leaflet before you start using this medicine. Keep the card for further reference if needed.

If your treating doctor prescribed you YERVOY in combination with OPDIVO (nivolumab), there is a card and patient safety information brochure for the combined treatment. The card and brochure contain important safety information, which you should know before starting and during treatment with YERVOY in combination with OPDIVO and which you should follow. Carefully read these materials and the patient leaflet before you start using this medicine. Keep the card and brochure for further reference, if needed.

1. What is this medicine intended for?

- 1. Unresectable** (that cannot be removed by surgery) **or metastatic** (that has spread to other parts of the body) **skin cancer called melanoma**
 - For the treatment of advanced (unresectable or metastatic) melanoma
 - For combined treatment with nivolumab in advanced (unresectable or metastatic) melanoma.
- 2. Advanced kidney cell cancer** (called renal cell carcinoma)
In combination with nivolumab in patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma.
- 3. MSI-H or dMMR metastatic colon or rectal cancer in adults and children 12 years of age and older**
In combination with nivolumab in case of advanced disease following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.
- 4. Metastatic non-small cell lung cancer**
In combination with nivolumab and 2 cycles of chemotherapy that contains platinum and another chemotherapy medicine (platinum-doublet chemotherapy), as first-line treatment of adults with metastatic or recurrent non-small cell lung cancer and with no EGFR or ALK genomic tumour aberrations.

5. **Liver cancer** (hepatocellular carcinoma)
In combination with nivolumab for liver cancer with mild liver impairment (Child-Pugh A) in patients who were previously treated with sorafenib.

Therapeutic group: antineoplastic

2. Before using this medicine:

Do not use this medicine if

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

Special warnings regarding use of this medicine:

Before treatment with YERVOY, tell your 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 myasthenia gravis (severe muscle weakness) or Guillain-Barré syndrome
- you are pregnant or plan to become pregnant - see the 'Pregnancy and breast-feeding' section
- you are breastfeeding or planning to breastfeed - see the 'Pregnancy and breast-feeding' 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

Your doctor will take blood tests before and during treatment with YERVOY.

Drug interactions

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

Pregnancy and breastfeeding:

YERVOY may harm your unborn baby.

Women of childbearing potential:

Your doctor will give you a pregnancy test before starting treatment with YERVOY.

- You must use effective contraception during treatment and for 3 months after administration of the last dose of YERVOY. Speak to your 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 your doctor immediately.
- Inform your doctor if you are breastfeeding or planning to breastfeed. It is not known if YERVOY can pass into your breast milk.
- Do not breastfeed during treatment with YERVOY and for 3 months after the final dose of YERVOY.

Driving and using machines:

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 your doctor before the medicine is administered.

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

This 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 to use this medicine?

Always use this medicine according to your doctor's instructions.

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

Only your doctor will determine your dose and duration of treatment.

Do not exceed the recommended dose.

- When YERVOY is given alone (as monotherapy), it is given directly into your vein through an intravenous line over 90 minutes.
- When YERVOY is given in combination with OPDIVO (nivolumab), OPDIVO 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 or 90 minutes on the same day.
- YERVOY in combination with OPDIVO (nivolumab) is usually given every 3 weeks for 4 treatment doses. After that, OPDIVO alone is usually given every 2 or 4 weeks.
 - For non-small cell lung cancer that has spread to other parts of your body, YERVOY is given every 6 weeks and OPDIVO (nivolumab) is given every 2 weeks for up to 2 years. You will also need chemotherapy every 3 weeks for 2 treatment cycles.
- Your doctor will decide how many treatments you need.
- Your doctor will do blood tests before starting and during treatment with YERVOY.
- If you cannot come in for a treatment scheduled for you, call your doctor as soon as possible to schedule a new date for the treatment.

If you have taken an overdose or if a child has accidentally swallowed some of this medicine, talk to a doctor or go to a hospital straight away and bring the medicine pack with you.

Adhere to the treatment as recommended by your 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 any further questions regarding use of this medicine, consult your doctor or pharmacist.

4. Side effects

Like with all medicines, using YERVOY may cause side effects in some users. Do not be alarmed by this list of side effects. You may not experience any of them.

YERVOY may cause serious side effects:

YERVOY is a medicine that may treat certain cancers by activating your immune system. YERVOY can cause your immune system to attack normal 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 have 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 OPDIVO (nivolumab).

Contact your doctor right away if you experience any new signs or symptoms or if signs or symptoms worsen, including:

Intestinal problems.

- diarrhoea (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 coloured)
- 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.

- headache 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
- your voice gets deeper
- dizziness or fainting
- changes in mood or behaviour, 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 your doctor right away for any new signs or symptoms 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 behaviour, 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 cell count, bruising

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

Your doctor will check you for these problems during your treatment with YERVOY. Your doctor may treat you with corticosteroid or hormone replacement medicines. Your doctor may delay or completely stop treatment with YERVOY if the side effects are severe.

Severe infusion-related reactions

Tell your 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). 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. Your 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
- diarrhoea
- nausea
- itching
- rash
- vomiting
- fever
- decreased appetite

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

- urticaria (hives)
- headache
- weight loss
- Inflammation of the colon (colitis)

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

- large intestinal ulcer
- esophagitis
- difficulty breathing due to fluid build-up 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
- edema
- rash
- itching
- dry skin
- diarrhoea
- nausea
- vomiting
- abdominal pain
- constipation
- swollen stomach due to build-up of fluid (ascites)
- dry mouth
- dyspepsia
- sores or ulcers in the mouth (stomatitis)
- pain in muscles, bones and joints
- cough, cough with phlegm
- shortness of breath, shortness of breath when exerting yourself
- inflammation of the lung tissue (pneumonitis)
- decreased appetite
- headache
- dizziness
- flu
- influenza-like illness
- weakness, generally feeling unwell
- chills
- low blood pressure
- low thyroid hormone levels [hypothyroidism (underactive thyroid)] that can lead to fatigue and weight gain
- high thyroid hormone levels [hyperthyroidism (overactive thyroid)] that can lead to rapid heart rate, sweating and weight loss
- adrenal insufficiency (decrease in the level of hormones secreted by the adrenal glands)
- decreased weight
- trouble sleeping
- abnormal laboratory test results

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

- upper respiratory tract infection
- diabetes
- inflammation of the colon (colitis)
- increased blood level of creatine phosphokinase
- pneumonia
- inflammation of the pituitary gland
- dehydration
- respiratory failure (extreme difficulty breathing)
- acute kidney injury
- liver problems
- oesophageal varices haemorrhage

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

- inflammation of the brain (encephalitis)

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

Side effects during combined treatment of YERVOY with OPDIVO (nivolumab) and chemotherapy

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

- feeling tired
- fever
- pain in muscles, bones and joints
- nausea
- diarrhoea
- constipation
- vomiting
- abdominal pain
- rash
- itching, including widespread itching
- hair loss
- decreased appetite
- cough
- shortness of breath
- low thyroid hormone levels [hypothyroidism (underactive thyroid)] that can lead to 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 (neutropenic fever)
- acute kidney injury
- inflammation of the lung tissue (pneumonitis)
- respiratory failure (extreme difficulty breathing)
- death due to side effects

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

These are not all the possible side effects of YERVOY.
For medical information regarding side effects, contact your doctor.

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 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 2°C - 8°C, for no more than 24 hours from the time of preparation to
the time of infusion.

6. Additional information:

In addition to the active ingredient, this 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 contents of the pack:

Clear to slightly opalescent, colourless to pale-yellow liquid. The liquid may contain amorphous particulates (small number).

YERVOY is available in a single-use 10 ml (50 mg) and a single-use 40 ml (200 mg) 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 Ministry of Health's National Drug Registry:
147-62-33522

Revised in June 2021 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.