

Package leaflet: Information for the user

YERVOY 5 mg/ml concentrate for solution for infusion ipilimumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What YERVOY is and what it is used for
2. What you need to know before you use YERVOY
3. How to use YERVOY
4. Possible side effects
5. How to store YERVOY
6. Contents of the pack and other information

1. What YERVOY is and what it is used for

YERVOY contains the active substance ipilimumab, a protein which helps your immune system to attack and destroy cancer cells by your immune cells.

Ipilimumab alone is used to treat advanced melanoma (a type of skin cancer) in adults and adolescents 12 years of age and older.

Ipilimumab in combination with nivolumab is used to treat

- advanced melanoma (a type of skin cancer) in adults and adolescents 12 years of age and older
- advanced renal cell carcinoma (advanced kidney cancer) in adults
- malignant pleural mesothelioma (a type of cancer that affects the lining of the lung) in adults
- advanced colorectal cancer (colon or rectal cancer) in adults
- advanced oesophageal cancer (gullet cancer) in adults.

Ipilimumab in combination with nivolumab and chemotherapy is used to treat advanced non-small cell lung cancer (a type of lung cancer) in adult.

As YERVOY may be given in combination with other anti-cancer medicines, it is important that you also read the package leaflet for these other medicines. If you have any questions about these medicines, please ask your doctor.

2. What you need to know before you use YERVOY

You should not be given YERVOY

- if you are **allergic** to ipilimumab or any of the other ingredients of this medicine (listed in Section 6 "Contents of the pack and other information"). **Talk to your doctor** if you are not sure.

Warnings and precautions

Talk to your doctor before using YERVOY as it may cause:

- **Problems with your heart** such as a change in the rhythm or rate of the heartbeat or an abnormal heart rhythm.

- **Inflammation of the intestines (colitis)** which can worsen to bleedings or bowel perforation. Signs and symptoms of colitis may include diarrhoea (watery, loose or soft stools), an increased number of bowel movements than usual, blood in your stools or darker-coloured stools, pain or tenderness in your stomach area.
- **Problems with your lungs** such as breathing difficulties or cough. These may be signs of inflammation of the lungs (pneumonitis or interstitial lung disease).
- **Inflammation of the liver (hepatitis)** that can lead to liver failure. Signs and symptoms of hepatitis may include eye or skin yellowing (jaundice), pain on the right side of your stomach area, tiredness.
- **Inflammation of the skin** that can lead to severe skin reaction (known as toxic epidermal necrolysis, Stevens-Johnson syndrome and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)). Signs and symptoms of severe skin reaction may include such as skin rash with or without itching, peeling of the skin, dry skin, fever, fatigue, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells) and effects on liver, kidneys or lungs. Please note that the reaction called DRESS may develop weeks or months after your last dose.
- **Inflammation of the nerves** that can lead to paralysis. Symptoms of nerve problems may include muscle weakness, numbness or tingling in your hands or feet, loss of consciousness or difficulty waking up.
- **Inflammation or problems with your kidneys.** Signs and symptoms may include abnormal kidney function tests, or decreased volume of urine.
- **Inflammation of hormone producing glands** (especially the pituitary, adrenal and thyroid glands) that may affect how these glands work. Signs and symptoms that your glands are not working properly may include headaches, blurry or double vision, tiredness, decreased sexual drive, behavioral changes.
- **Type 1 Diabetes, including diabetic ketoacidosis** (acid in the blood produced from diabetes).
- **Inflammation of the muscles** such as myocarditis (inflammation of the heart muscle), myositis (inflammation of the muscles) and rhabdomyolysis (stiffness in muscles and joints, muscle spasm). Signs and symptoms may include muscle pain, stiffness, weakness, chest pain, or severe fatigue.
- **Inflammation of the eyes.** Signs and symptoms may include redness in the eye, pain in the eye, vision problems, blurry vision or temporary loss of sight.
- **Haemophagocytic lymphohistiocytosis.** A rare disease in which our immune system makes too many of otherwise normal infection fighting cells called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems.
- **Organ transplant rejection.**

Tell your doctor immediately if you have any of these signs or symptoms or they get worse. **Do not try to treat your symptoms with other medicines.** Your doctor may give you other medicines in order to prevent more severe complications and reduce your symptoms, withhold the next dose of YERVOY, or stop your treatment with YERVOY altogether.

Please note that these signs and symptoms are **sometimes delayed**, and may develop weeks or months after your last dose. Before treatment, your doctor will check your general health. You will also have **blood tests** during treatment.

Check with your doctor or nurse before you are given YERVOY

- if you have an **autoimmune disease** (a condition where the body attacks its own cells);
- if you have, or have ever had, **chronic viral infection of the liver**, including hepatitis B (HBV) or hepatitis C (HCV);
- if you have **human immunodeficiency virus (HIV)** infection or acquired immune deficiency syndrome (AIDS).
- if you have previously experienced a severe skin adverse reaction on a prior cancer therapy.
- if you have any history of inflammation of the lungs

Children and adolescents

YERVOY should not be used in children and adolescents below 18 years of age except for adolescents 12 years of age and older with melanoma.

Other medicines and YERVOY

Before you are given YERVOY, tell your doctor

- if you are taking any medicines that suppress your immune system, such as corticosteroids. These medicines may interfere with the effect of YERVOY. However, once you are treated with YERVOY, your doctor may give you corticosteroids to reduce the side-effects that you may have with YERVOY.
- if you are taking any medicines that stop your blood from clotting (anticoagulants). These medicines may increase the likelihood of bleeding in the stomach or intestine, which is a side-effect of YERVOY.
- if you have recently been prescribed Zelboraf (vemurafenib, another medicine for the treatment of skin cancer). When YERVOY is given following prior vemurafenib there may be an increased risk of skin side-effects.

Also tell your doctor if you are taking or have recently taken any other medicines.

Do not take any other medicines during your treatment without talking to your doctor first. Based on early data, the combination of YERVOY (ipilimumab) and vemurafenib is not recommended due to increased toxicity to the liver.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant, if you are planning to become pregnant, or if you are breast-feeding.

You must not use YERVOY if you are pregnant unless your doctor specifically recommends it. The effects of YERVOY in pregnant women are not known, but it is possible that the active substance, ipilimumab, could harm an unborn baby.

- You must use **effective contraception** while you are being treated with YERVOY if you are a woman who could become pregnant.
- If you become pregnant while using YERVOY **tell your doctor**.

It is not known whether ipilimumab gets into breast milk. However, significant exposure of ipilimumab to the infant through breast milk is not expected and no effects on the breast-fed infant are anticipated. Ask your doctor if you can breast-feed during or after treatment with YERVOY.

Driving and using machines

Do not drive, cycle or use machines after you have been given YERVOY unless you are sure you are feeling well. Feeling tired or weak is a very common side effect of YERVOY. This can affect your ability to drive, cycle or to use machines.

YERVOY contains sodium

Tell your doctor if you are on a low-sodium (low-salt) diet before you are given YERVOY.

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

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

3. How to use YERVOY

How YERVOY is given

YERVOY will be given to you in a hospital or clinic under the supervision of an experienced doctor.

When YERVOY is given alone for the treatment of skin cancer, YERVOY will be given to you as an infusion (a drip) into a vein (intravenously) over a period of 30 minutes.

When YERVOY is given in combination with nivolumab for the treatment of skin cancer, you will be given an infusion over a period of 30 minutes every 3 weeks for the first 4 doses (combination phase). Thereafter, nivolumab will be given as an infusion over a period of 30 or 60 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving (single-agent phase).

When YERVOY is given in combination with nivolumab for the treatment of advanced kidney cancer, you will be given an infusion over a period of 30 minutes every 3 weeks for the first 4 doses (combination phase). Thereafter, nivolumab will be given as an infusion over a period of 30 or 60 minutes, every 2 weeks or 4 weeks, depending on the dose you are receiving (single-agent phase).

When YERVOY is given in combination with nivolumab for the treatment of advanced colon or rectal cancer in adults, you will be given an infusion over a period of 30 minutes every 3 weeks for the first 4 doses (combination phase). Thereafter, nivolumab will be given as an infusion over a period of 30 minutes, every 2 weeks (single-agent phase).

When YERVOY is given in combination with nivolumab for the treatment of malignant pleural mesothelioma or advanced oesophageal cancer, you will be given an infusion over a period of 30 minutes every 6 weeks.

When YERVOY is given in combination with nivolumab and chemotherapy for the treatment of advanced non-small cell lung cancer, you will be given an infusion over a period of 30 minutes every 6 weeks. After completion of 2 cycles of chemotherapy, ipilimumab will be given in combination with nivolumab as an infusion over a period of 30 minutes every 6 weeks.

How much YERVOY is given

When YERVOY is given alone for the treatment of skin cancer, the recommended dose is 3 mg of ipilimumab per kilogram of your body weight.

The amount of YERVOY you will be given will be calculated based on your body weight. Depending on your dose, some or all of the content of the YERVOY vial may be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection or 50 mg/ml (5%) glucose solution for injection before use. More than one vial may be necessary to obtain the required dose.

You will be treated with YERVOY once every 3 weeks, for a total of 4 doses. You may notice the appearance of new lesions or growth of existing lesions on your skin, which can be expected when you are being treated with YERVOY. Your doctor will continue giving you YERVOY for a total of 4 doses, depending on your tolerance to the treatment.

When YERVOY is given in combination with nivolumab for the treatment of skin cancer in adults and adolescents 12 years of age and older, the recommended dose of YERVOY is 3 mg of ipilimumab per

kilogram of your body weight every 3 weeks for the first 4 doses (combination phase). Thereafter the recommended dose of nivolumab (single-agent phase) is 240 mg given every 2 weeks or 480 mg given every 4 weeks in adults and adolescents 12 years of age and older and weighing at least 50 kg or 3 mg of nivolumab per kilogram of your body weight given every 2 weeks or 6 mg of nivolumab per kilogram of your body weight given every 4 weeks for adolescents 12 years of age and older and weighing less than 50 kg.

When YERVOY is given in combination with nivolumab for the treatment of advanced kidney cancer, the recommended dose of YERVOY is 1 mg of ipilimumab per kilogram of your body weight every 3 weeks for the first 4 doses (combination phase). Thereafter, the recommended dose of nivolumab is 240 mg given every 2 weeks or 480 mg given every 4 weeks (single-agent phase).

When YERVOY is given in combination with nivolumab for the treatment of advanced colon or rectal cancer, the recommended dose of YERVOY is 1 mg of ipilimumab per kilogram of your body weight every 3 weeks for the first 4 doses (combination phase). Thereafter, the recommended dose of nivolumab is 240 mg given every 2 weeks (single-agent phase).

When YERVOY is given in combination with nivolumab for the treatment of malignant pleural mesothelioma or advanced oesophageal cancer, the recommended dose of YERVOY is 1 mg of ipilimumab per kilogram of your body weight every 6 weeks.

When YERVOY is given in combination with nivolumab and chemotherapy for the treatment of advanced non-small cell lung cancer, the recommended dose of YERVOY is 1 mg of ipilimumab per kilogram of your body weight. You will be given an infusion over a period of 30 minutes, every 6 weeks.

If you miss a dose of YERVOY

It is very important for you to keep all your appointments to receive YERVOY. If you miss an appointment, ask your doctor when to schedule your next dose.

If you stop using YERVOY

Stopping your treatment may stop the effect of the medicine. Do not stop treatment with YERVOY unless you have discussed this with your doctor.

If you have any further questions about your treatment or the use of this medicine, ask your doctor.

When YERVOY is given in combination with nivolumab or in combination with nivolumab and chemotherapy, you will first be given nivolumab followed by YERVOY and then by chemotherapy.

Please refer to the package leaflet of the other anti-cancer medicines in order to understand the use of these other medicines. If you have questions about these medicines, please ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your doctor will discuss these with you and will explain the risks and benefits of your treatment.

Be aware of important symptoms of inflammation

YERVOY acts on your immune system and may cause **inflammation** in parts of your body. Inflammation may cause serious damage to your body and some inflammatory conditions may be life-threatening.

The following side effects have been reported in patients receiving 3 mg/kg ipilimumab alone:

Very common (may affect more than 1 in 10 people)

- loss of appetite

- diarrhoea (watery, loose or soft stools), vomiting or feeling sick (nausea), constipation, stomach pain
- skin rash, itching
- pain in the muscles, bones, ligaments, tendons and nerves
- feeling tired or weak, reaction at site of injection, fever, oedema (swelling), pain

→ **Tell your doctor immediately** if you get any of these side effects.

Do not try to treat your symptoms with other medicines.

Common (may affect up to 1 in 10 people)

- serious bacterial infection of the blood (sepsis), infection of the urinary tract, infection of the respiratory tract
- tumour pain
- a decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- underactive function of the thyroid gland which can cause tiredness or weight gain, underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain
- dehydration
- confusion, depression
- excessive accumulation of fluid in the brain, damage to the nerves (causing pain, weakness and cramps), dizziness, headache
- blurred vision, pain in the eye
- irregular or abnormal heart beat
- low blood pressure, temporary redness of the face and neck, feeling of intense heat with sweating and rapid heart beat
- shortness of breath (dyspnoea), cough, hay fever
- bleeding in the stomach or intestine, inflammation of the intestines (colitis), heartburn, mouth ulcers and cold sores (stomatitis)
- abnormal function of the liver
- inflammation of the inner surface lining of a particular organ
- inflammation and redness of the skin, skin colour change in patches (vitiligo), hives (itchy, bumpy rash), hair loss or thinning, excessive sweating at night, dry skin
- pain in muscles and joints (arthralgia), muscle spasms, inflammation of the joints (arthritis)
- kidney function failure
- shivering, lack of energy
- flu-like illness
- decrease in body weight

→ **Tell your doctor immediately** if you get any of these side effects.

Do not try to treat your symptoms with other medicines.

Uncommon (may affect up to 1 in 100 people)

- serious bacterial infection of the blood (septic shock), inflammation around the brain or spinal cord, inflammation of the stomach and intestines, inflammation of bowel wall (causing fever, vomiting and stomach pain), lung infection (pneumonia)
- a group of symptoms due to cancer in the body such as high blood levels of calcium and cholesterol, and low blood levels of sugar (paraneoplastic syndrome)
- increase of eosinophils (type of white blood cells)
- allergic reaction
- decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), overactive function of the thyroid gland, which can cause rapid heart rate, sweating and weight loss, defect of the glands producing sex hormones
- decreased function of the adrenal glands caused by an underactive hypothalamus (part of the brain)
- a group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome).

- changes in mental health, lowered sex drive
- severe and possibly fatal inflammation of the nerves causing pain, weakness or paralysis in the extremities (Guillain-Barré syndrome), fainting, inflammation of the nerves within the brain, difficulty in coordinating movements (ataxia), shaking, brief involuntary muscle contraction, difficulty in speaking
- inflammation of the eye (conjunctivitis), bleeding in the eye, inflammation of the coloured part of the eye, reduced vision, a foreign body sensation in the eyes, swollen runny eyes, swelling of the eye, inflammation of the eyelids
- inflammation of the blood vessels, disease of the blood vessels, restriction in the blood supply to the extremities, low blood pressure when standing up
- extreme difficulty in breathing, fluid accumulation in the lungs, inflammation of the lungs
- bowel perforation, inflammation of the small intestine, inflammation of the bowel or the pancreas (pancreatitis), peptic ulcer, inflammation of the food pipe, blockage of the intestines, inflammation of the anus and the rectal wall (marked by bloody stools and a frequent urge to defecate)
- liver failure, inflammation of the liver, enlarged liver, yellowing of the skin or eyes (jaundice)
- severe and possibly fatal peeling of the skin (toxic epidermal necrolysis)
- inflammation of the muscles causing pain or stiffness in the hip and shoulder
- inflammation of the kidney, or the central nervous system
- multi organ inflammation
- inflammation of skeletal muscles
- muscle weakness
- kidney disease
- absence of menstrual periods
- multi organ dysfunction, reaction related to infusion of the medicine
- change in hair colour
- inflammation of the bladder, signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen

➔ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Rare (may affect up to 1 in 1,000 people)

- inflammatory disease of blood vessels (most commonly head arteries)
- swelling of the thyroid gland (thyroiditis)
- skin disease characterized by dry red patches covered with scales (psoriasis)
- inflammation and redness of the skin (erythema multiforme)
- a type of severe skin reaction characterized by rash accompanied by one or more of the following features: fever, swelling of the face or lymph glands, increase of eosinophils (type of white blood cells), effects on liver, kidneys or lungs (a reaction called DRESS).
- an inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome), loosening of membrane at the back of the eye (serous retinal detachment)
- symptoms of type 1 diabetes or diabetic ketoacidosis include feeling more hungry or thirsty than usual, needing to urinate more often, weight loss, feeling tired, feeling sick, stomach pain, fast and deep breathing, confusion, unusual sleepiness, a sweet smell to your breath, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat
- muscle weakness and tiredness without atrophy (myasthenia gravis)

➔ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Very rare (may affect up to 1 in 10,000 people)

- serious, potential life-threatening allergic reaction

➔ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

In addition, the following uncommon (may affect up to 1 in 100 people) side effects have been reported in patients who received doses other than 3 mg/kg of YERVOY in clinical trials:

- triad of symptoms (meningism): neck stiffness, intolerance of bright light and headache, flu-like discomfort
- inflammation of the heart muscle, weakness of the heart muscle, fluid around the heart
- inflammation of the liver or the pancreas, nodules of inflammatory cells in various organs of your body
- infection within the abdomen
- painful skin lesions of the arms and legs and face (erythema nodosum)
- overactive pituitary gland
- decreased function of the parathyroid gland
- inflammation of the eye, eye muscle inflammation
- decreased hearing
- poor blood circulation which makes toes and fingers numb or pale
- damage to the tissues of the hands and feet resulting in redness, swelling and blisters

→ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):

- organ transplant rejection
- a type of skin blistering disease (called pemphigoid)
- a condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis). Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems.
- pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation (myelitis)

→ **Tell your doctor immediately** if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Changes in test results

YERVOY may cause changes in the results of tests carried out by your doctor. These include:

- a variation in the number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- an abnormal variation of hormones and liver enzyme levels in the blood
- abnormal liver function test
- abnormal levels of calcium, sodium, phosphate or potassium in the blood
- presence of blood or proteins in the urine
- an abnormally high alkalinity of the blood and other body tissues
- kidneys unable to remove acids from blood normally
- presence of antibodies in the blood against some of your own cells

The following side effects have been reported **with ipilimumab in combination with other anti-cancer medicines** (the frequency and severity of side effects may vary with the combination of anti-cancer medicines received):

Very common (may affect more than 1 in 10 people)

- infections of the upper respiratory tract
- underactive thyroid gland (which can cause tiredness or weight gain)
- a decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)

- loss of appetite, high (hyperglycaemia) or low (hypoglycaemia) sugar levels in the blood
- headache, dizziness
- shortness of breath (dyspnoea), cough
- diarrhoea (watery, loose or soft stools), vomiting or feeling sick (nausea), stomach pain, constipation
- skin rash sometimes with blisters, itching
- pain in the muscles and bones (musculoskeletal pain), painful joints (arthralgia)
- feeling tired or weak, fever, oedema (swelling)

→ Tell your doctor immediately if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Common (may affect up to 1 in 10 people)

- lung infection (pneumonia), bronchitis, inflammation of the eye (conjunctivitis)
- increase of eosinophils (type of white blood cells)
- allergic reaction, reactions related to the infusion of the medicine
- overactive thyroid gland (which can cause rapid heart rate, sweating and weight loss), decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), underactive function (hypopituitarism) or inflammation (hypophysitis) of the pituitary gland situated at the base of the brain, swelling of the thyroid gland, diabetes
- dehydration, decreased levels of albumin and phosphate in the blood, decrease in body weight
- inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs)
- blurred vision, dry eye
- rapid heart beat, changes in the rhythm or rate of the heartbeat, irregular or abnormal heart beat
- high blood pressure (hypertension)
- inflammation of the lungs (pneumonitis, characterised by coughing and difficulty breathing), fluid around the lungs
- inflammation of the intestines (colitis), mouth ulcers and cold sores (stomatitis), inflammation of the pancreas (pancreatitis), dry mouth, inflammation of the stomach (gastritis)
- inflammation of the liver
- skin colour change in patches (vitiligo), redness of the skin, unusual hair loss or thinning, hives (itchy, bumpy rash), dry skin
- inflammation of the joints (arthritis), muscle spasm, muscle weakness
- kidney failure (including abrupt loss of kidney function)
- pain, chest pain, chills

→ Tell your doctor immediately if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Uncommon (may affect up to 1 in 100 people)

- decrease in neutrophils with fever
- acid in the blood produced from diabetes (diabetic ketoacidosis)
- increased acid levels in the blood
- inflammation of the brain; damage to nerves causing numbness and weakness (polyneuropathy); foot drop (peroneal nerve palsy); inflammation of the nerves caused by the body attacking itself, causing numbness, weakness, tingling or burning pain (autoimmune neuropathy); muscle weakness and tiredness without atrophy (myasthenia gravis)
- inflammation of the eye which causes redness or pain
- irregular or abnormal heart beat, inflammation of the heart muscle, slow heart rate
- inflammation of the duodenum
- skin disease with thickened patches of red skin, often with silvery scales (psoriasis), severe condition of the skin that causes red, often 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 and possibly fatal peeling of the skin (Stevens-Johnson syndrome)

- aching muscles, muscle tenderness or weakness, not caused by exercise (myopathy), inflammation of the muscles (myositis), inflammation of the muscles causing pain or stiffness (polymyalgia rheumatica)
- inflammation of the kidney

→ Tell your doctor immediately if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Rare (may affect up to 1 in 1000 people)

- temporary and reversible non-infectious inflammation of the protective membranes surrounding the brain and spinal cord (aseptic meningitis)
- chronic diseases associated with a build-up of inflammatory cells in various organs and tissues, most commonly the lungs (sarcoidosis)
- decreased function of the parathyroid gland
- temporary inflammation of the nerves that causes pain, weakness and paralysis in the extremities (Guillain-Barré syndrome), inflammation of the nerves
- pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation (myelitis/transverse myelitis)
- bowel perforation
- severe and possibly fatal peeling of the skin (toxic epidermal necrolysis), changes in any area of the skin and/or genital area that are associated with drying out, thinning, itching and pain (lichen sclerosus or other lichen disorders)
- chronic disease of joints (spondyloarthritis), disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome), stiffness in muscles and joints, muscle spasm (rhabdomyolysis)
- an inflammatory disorder (most likely of autoimmune origin) affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada syndrome), loosening of membrane at the back of the eye (serous retinal detachment)
- inflammation of the bladder, signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen

→ Tell your doctor immediately if you get any of these side effects.
Do not try to treat your symptoms with other medicines.

Other side effects that have been reported with frequency not known (cannot be estimated from the available data):

- organ transplant rejection
- a group of metabolic complications occurring after cancer treatment characterised by high blood levels of potassium and phosphate, and low blood levels of calcium (tumour lysis syndrome)
- inflammation of the covering of the heart and accumulation of fluid around the heart (pericardial disorders)
- a condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (called haemophagocytic lymphohistiocytosis). Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems

Changes in test results

YERVOY in combination may cause changes in the results of tests carried out by your doctor. These include:

- abnormal liver function tests (increased amounts of the liver enzymes aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, or alkaline phosphatase in your blood, higher blood levels of the waste product bilirubin)
- abnormal kidney function tests (increased amounts of creatinine in your blood)
- an increased level of the enzyme that breaks down fats and of the enzyme that breaks down starch
- increased or decreased amount of calcium or potassium

- increased or decreased blood levels of magnesium or sodium
- increased amount of thyroid stimulating hormone

Reporting of side effects

If you get any side effects, **talk to your doctor**. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

5. How to store YERVOY

Keep this medicine out of the sight and reach of children.

Do not use this medicine 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.

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Store in the original package in order to protect from light.

Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What YERVOY contains

- The active substance is ipilimumab.
Each ml of concentrate contains 5 mg of ipilimumab.
Each 10 ml vial contains 50 mg of ipilimumab.
Each 40 ml vial contains 200 mg of ipilimumab.
- The other ingredients are Tris-hydrochloride, sodium chloride (see section 2 "YERVOY contains sodium"), mannitol (E421), pentetic acid, polysorbate 80, sodium hydroxide, hydrochloric acid and water for injections.

What YERVOY looks like and contents of the pack

YERVOY concentrate for solution for infusion is clear to slightly opalescent, colourless to pale yellow and may contain light (few) particulates.

It is available in packs containing either 1 glass vial of 10 ml or 1 glass vial of 40 ml.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer

Swords Laboratories Unlimited Company T/A Bristol-Myers Squibb Cruiserath Biologics
Cruiserath Road, Mulhuddart
Dublin 15, D15 H6EF
Ireland

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The following information is intended for healthcare professionals only:

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

Calculating the dose:

Ipilimumab monotherapy or ipilimumab in combination with nivolumab:

The **prescribed dose** for the patient is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given. More than one vial of YERVOY concentrate may be needed to give the total dose for the patient.

- Each 10 ml vial of YERVOY concentrate provides 50 mg of ipilimumab; each 40 ml vial provides 200 mg of ipilimumab.
- The **total ipilimumab dose** in mg = the patient's weight in kg × the prescribed dose in mg/kg.
- The **volume of YERVOY concentrate** to prepare the dose (ml) = the total dose in mg, divided by 5 (the YERVOY concentrate strength is 5 mg/ml).

Preparing the infusion:

Take care to ensure aseptic handling when you prepare the infusion.

YERVOY can be used for intravenous administration either:

- **without dilution**, after transfer to an infusion container using an appropriate sterile syringe; or
- **after diluting** to up to 5 times the original volume of concentrate (up to 4 parts of diluent to 1 part of concentrate). The final concentration should range from 1 to 4 mg/ml. To dilute the YERVOY concentrate, you can use either:
 - sodium chloride 9 mg/ml (0.9%) solution for injection; or
 - 50 mg/ml (5%) glucose solution for injection

STEP 1

- Allow the appropriate number of vials of YERVOY to stand at room temperature for approximately 5 minutes.
- Inspect the YERVOY concentrate for particulate matter or discoloration. YERVOY concentrate is a clear to slightly opalescent, colourless to pale yellow liquid that may contain light (few) particulates. Do not use if unusual amount of particles and signs of discoloration are present.
- Withdraw the required volume of YERVOY concentrate using an appropriate sterile syringe.

STEP 2

- Transfer the concentrate into a sterile, evacuated glass bottle or IV bag (PVC or non-PVC).
- If applicable, dilute 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.

Administration:

The YERVOY infusion must not be administered as an intravenous push or bolus injection. Administer the YERVOY infusion intravenously **over a period of 30 minutes**.

The YERVOY infusion should not be infused at the same time in the same intravenous line with other agents. Use a separate infusion line for the infusion.

Use an infusion set and an in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm).

The YERVOY infusion is compatible with:

- PVC infusion sets
- Polyethersulfone (0.2 µm to 1.2 µm) and nylon (0.2 µm) in-line filters

Flush the line with sodium chloride 9 mg/ml (0.9%) solution for injection or 50 mg/ml (5%) glucose solution for injection at the end of the infusion.

Storage conditions and shelf life:

Unopened vial

YERVOY 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. YERVOY should not be frozen.

Do not use YERVOY after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

YERVOY infusion

From a microbiological point of view, once opened, the medicine **should be infused or diluted and infused immediately**. The chemical and physical in-use stability of the undiluted or diluted infusion solution (between 1 and 4 mg/ml) has been demonstrated for 24 hours at room temperature (20°C to 25°C) or when refrigerated (2°C to 8°C). If not used immediately, the infusion solution (undiluted or diluted) must be used within 24 hours when stored either under refrigeration (2°C to 8°C) or at room temperature (20°C to 25°C). Other in-use storage time and conditions are the responsibility of the user.

Disposal:

Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.