NOVARTIS

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

The medicine is dispensed with a doctor's prescription only.

Kymriah® 1.2×10⁶ – 6×10⁸ cells Dispersion for intravenous infusion

Active ingredient:
Tisagenlecleucel 1.2×10⁶ to 6×10⁸ CAR-positive viable T cells

Inactive and allergenic ingredients: see "Important information about some of the ingredients of the medicine" in section 2 as well as section 6 "Further information".

Read the 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.

The information in this leaflet is intended for you or your child.

In addition to this leaflet, Kymriah has a Patient Information Brochure that contains important safety information which you must know and adhere to before starting and during treatment, as well as a Patient Alert Card.

Read the informational materials and the Patient Leaflet before starting to use the preparation. Keep the card and brochure for further reading, if necessary.

1. WHAT IS THE MEDICINE INTENDED FOR?

Kymriah is intended to treat:
1. Children and young adults, up to and including the age of 25 years, with B-cell acute lymphoblastic leukaemia, expressing CD19 (CD19+), that is resistant, recurrent after a transplant or recurring for the second time or more.
2. Adults with diffuse large B-cell lymphoma, that is resistant or recurrent after at least two lines of systemic treatment.
Restriction: Kymriah is not intended for patients with primary or secondary central nervous system lymphoma.
3. Adults with follicular lymphoma, that is resistant or recurrent after at least two lines of systemic treatment.

Therapeutic group: antineoplastic medicines

What is Kymriah
Kymriah, also known as tisagenlecleucel, is made from a certain type of your own white blood cells called T cells. T cells are important for your immune system (the body's defenses) to work properly.

How does Kymriah work?
The T cells are taken from your blood and a new gene is inserted into them so that they can target the cancer cells in your body. When Kymriah is infused into your blood, the engineered T cells will find the cancer cells and kill them.

If you have questions about how Kymriah works or why it has been prescribed for you, ask the doctor.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:
- you are sensitive (allergic) to the active ingredient tisagenlecleucel or to any of the additional ingredients contained in the medicine (appearing in section 6).
- you cannot receive a treatment called lymphodepleting chemotherapy, which reduces the number of white blood cells in your blood.

Special warnings regarding use of the medicine
Kymriah is made from your white blood cells and intended for you only.
Patients treated with Kymriah may develop new types of cancers. There have been reports of patients developing cancer, beginning in a type of white blood cells called T-cells, after treatment with Kymriah and similar medicines. Talk to your doctor if you experience any new swelling of your glands (lymph nodes) or changes in your skin such as new rashes or lumps.
You might be asked to enrol in a registry for at least 15 years in order to better understand the long-term effects of Kymriah.

Before treatment with Kymriah, tell the doctor if:
- You have undergone a stem cell transplant in the last 4 months. Your doctor will check if you have signs or symptoms of graft-versus-host disease. This happens when the transplanted cells attack your body, and cause symptoms such as rash, nausea, vomiting, diarrhea and bloody stools.
- You have problems with functioning of the lung, kidney, liver, central nervous system, the heart or with blood pressure (low or high). Patients with problems in these systems are more likely to suffer from the side effects described in section 4 "Side effects" and may require closer supervision.
- You noticed worsening of the symptoms of your cancer. If you have leukemia, this might include fever, feeling weak, bleeding gums, bruising. If you have lymphoma, this might include unexplained fever, feeling weak, night sweats, sudden weight loss.
- You have an infection. The infection will be treated before the Kymriah infusion.
- You have had a hepatitis B, hepatitis C or human immunodeficiency virus (HIV) infection.
- You are pregnant, think you may be pregnant, or plan to become pregnant (see sections "Pregnancy, breastfeeding and fertility" and "Contraception for women and men" below).
- You received a vaccination in the past 6 weeks or are planning to receive one in the next few months.

If any of the above-mentioned apply to you (or you are not sure), talk to your doctor before receiving Kymriah.

Tests and follow-up
Before receiving Kymriah your doctor will:
- Check your lungs, heart and blood pressure.
- Look for signs of infection; any infection will be treated before you receive Kymriah.
- Check if your lymphoma or leukaemia is getting worse.
- Look for signs of graft-versus-host disease that can happen after a transplant.
- Check the uric acid in your blood and how many cancer cells there are in your blood. This will show if you are likely to develop a condition called tumor lysis syndrome. You may be given medicines to help prevent this condition.
- Check if you have hepatitis B, hepatitis C or human immunodeficiency virus (HIV) infection.

After you have been given Kymriah
Tell your doctor immediately if you have any of the following:
- Fever, which may be a symptom of an infection. The doctor will regularly check your blood counts, as the number of blood cells and other blood components may decrease.
- Take your temperature twice a day, for 3-4 weeks after treatment with Kymriah. If your temperature is high, refer to the doctor immediately.
- Altered or decreased consciousness, delirium, anxiety, dizziness, tremor, headache, confusion, agitation, seizures, difficulty speaking and understanding, and/or loss of balance. These effects usually occur within the first 8 weeks after the infusion, but they can occur after too. These may be symptoms of a condition called immune effector cell-associated neurotoxicity syndrome (ICANS).
- Extreme tiredness, weakness and shortness of breath, which may be symptoms of red blood cell deficiency.
- Bleeding or bruising more easily, which may be symptoms of a low level of blood cells known as platelets.

The results of some types of HIV testing may be affected – ask your doctor about this.

Your doctor will regularly monitor your blood counts after you receive Kymriah as you may experience a reduction in the number of blood cells and other blood components.

Do not donate blood, organs, tissues or cells for transplants.

Additional warnings and guidelines:
- Patients treated with Kymriah may develop secondary tumors or recurrence of their disease.
- After treatment with Kymriah and complete recovery, you may suffer from hypogammaglobulinemia (a deficiency of the gamma-globulin protein in the blood) and agammaglobulinemia (a condition in which there is complete deficiency of immunoglobulins, proteins produced by immune system cells).

Tests and follow-up
After receiving Kymriah, your doctor will:
- Refer you to be tested for secondary tumors for the rest of your life.
- Refer you to be tested for immunoglobulin levels (proteins produced by the cells of the immune system).

Children and adolescents
- B-cell acute lymphoblastic leukaemia: There are no established data from clinical studies in children below the age of 3.
- Diffuse large B-cell lymphoma and follicular lymphoma: Do not use Kymriah to treat DLBCL (diffuse large B-cell lymphoma) or FL (follicular lymphoma) in children and adolescents below the age of 18, since the preparation has not been studied in this age group.

Drug interactions
If you are taking, or have recently taken, or if you may take, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor. This is because other medicines can affect the way Kymriah works.
In particular, you must not receive certain vaccines called live vaccines:
- in the 6 weeks before you receive chemotherapy (called lymphodepleting chemotherapy) that is intended to prepare your body for receiving Kymriah cells.
- during Kymriah treatment.
- after the treatment, while the immune system is recovering.

Talk to your doctor if you need to receive any vaccination.
Before you receive Kymriah, inform your doctor if you are taking any medicines that weaken the immune system such as corticosteroids, since these medicines may interfere with the effect of Kymriah.

Pregnancy, breastfeeding and fertility
If you are pregnant or breastfeeding, may be pregnant or are planning to become pregnant (including women of child-bearing age who do not use contraceptive measures), consult with your doctor before receiving this medicine. This is because the effects of Kymriah in pregnant or breastfeeding women are not known, and it may harm your unborn baby or your newborn or infant.
- If you become pregnant or think you may be pregnant after treatment with Kymriah, talk your doctor immediately.
- Your doctor will instruct you to perform a pregnancy test before starting treatment. Treatment will only be given on the condition that the test is negative for pregnancy.

Contraception for women and men
Discuss pregnancy with your doctor if you have received Kymriah.

Driving and operating machinery
Some people may have problems such as altered or decreased consciousness, confusion and seizures after being given Kymriah. Therefore, do not drive, use machines, or take part in activities that require alertness in the 8 weeks following infusion.

Important information about some of the ingredients of the medicine
Kymriah contains sodium, dimethylsulfoxide (DMSO), dextran 40 and potassium.
This medicine contains 24.3 to 121.5 mg sodium (main component of cooking/table salt) per dose. This is equivalent to 1 to 6% of the recommended maximum daily dietary intake of sodium for an adult. This medicine contains dextran 40 and DMSO (substances used to preserve frozen cells), both of which can sometimes cause difficulty breathing and/or dizziness (possible symptoms of serious allergic or hypersensitivity reactions). You should be closely monitored during the infusion period.
This medicine contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially "potassium free".

3. HOW SHOULD YOU USE THE MEDICINE?

Kymriah is always given by a doctor and as per his instructions, in a medical center qualified for Kymriah treatment.
The dosage and treatment regimen will be determined by the doctor only.

Collecting blood to make Kymriah
Kymriah is made from your own white blood cells.
- Your doctor will take a certain amount of your blood using a catheter placed in your vein (a procedure called leukapheresis). Some of your white blood cells will be separated from your blood and the rest of your blood will be returned to your vein. This procedure can take 3 to 6 hours and may need to be repeated.
- Your white blood cells will be frozen and sent away to make Kymriah. Preparation of Kymriah usually takes about 3 to 4 weeks, but the duration may vary.
- Kymriah is a treatment that is manufactured specifically for you.
- Before receiving Kymriah, your doctor may give you a type of treatment called lymphodepleting chemotherapy for several days to prepare your body for Kymriah treatment.

Cancer treatment while Kymriah is being made
During the period while Kymriah is being made, your lymphoma or leukaemia may get worse and your doctor may decide to use an additional treatment (known as "bridging therapy") to stabilise your cancer by stopping new cancer cells from developing. This treatment may lead to side effects and these may be severe or life-threatening. Your doctor will explain to you the potential side effects of this treatment.

Other medicines given immediately before Kymriah treatment
During the 30 to 60 minutes before receiving Kymriah, you may be given additional medicines. This is to prevent infusion reactions and fever. These additional medicines may include:
- Paracetamol
- Antihistamine medicines such as diphenhydramine.

How Kymriah is given
- Your doctor will check that the personal patient identifiers that appear on the Kymriah bag match yours.
- Your doctor will give you Kymriah by infusion, which means it will be given as a drip through a tube inserted into your vein. This procedure usually takes less than one hour. During the infusion your doctor will check if you have difficulty breathing or dizziness (possible symptoms of an allergic reaction).
- Kymriah is a one-time treatment.

After receiving Kymriah
You must stay up to a two-hour drive away from the hospital where you received the treatment, for at least 4 weeks after receiving Kymriah treatment. Your doctor will recommend that you return to the hospital daily, for at least 10 days after receiving the treatment, and will consider whether you need to be hospitalized for the first 10 days after receiving the infusion. This is so your doctor will be able to check if the treatment is working and can help you in case you have any side effects.
Adhere to the treatment regimen recommended by the doctor.
If you have further questions regarding use of the medicine, consult the doctor.

If you miss an appointment
If you were scheduled for an appointment and you missed it, contact your doctor or hospital as soon as possible to set a new date.

4. SIDE EFFECTS

As with any medicine, use of Kymriah 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.
Refer to a doctor immediately if you get any of the following side effects after receiving the Kymriah infusion. They usually happen in the first 8 weeks after the infusion, but can also develop later:

Very common side effects (effects that occur in more than one user in ten)
- high fever and chills. These may be symptoms of a serious condition called cytokine release syndrome, which may be life-threatening or fatal. Other symptoms of cytokine release syndrome are breathing difficulties, nausea, vomiting, diarrhea, loss of appetite, fatigue, muscle pain, joint pain, swelling, low blood pressure, fast heartbeat, headache, heart, lung and kidney failure and liver injury. These symptoms almost always occur within the first 14 days after treatment with Kymriah, but in some patients can also develop later.
- problems such as altered thinking or decreased consciousness, loss of contact with reality, confusion, agitation, seizures, difficulty speaking and understanding speech, difficulty walking. These can be symptoms of a condition called immune effector cell-associated neurotoxicity syndrome (ICANS). These symptoms mostly occur within the first 8 weeks after treatment with Kymriah, but in some patients can also develop later.
- feeling warm, fever, chills or shivering, sore throat or mouth ulcers may be signs of an infection. Some infections may be life-threatening or fatal.

Common side effects (effects that occur in 1-10 in 100 users)
- Rapid breakdown of tumor cells causing release of their contents into the bloodstream. This can interfere with the functioning of various organs in the body, especially the kidneys, heart and nervous system (tumor lysis syndrome).

Other side effects
Other side effects are listed below. If these side effects become severe or serious, inform the doctor immediately.

Very common side effects (effects that occur in more than one user in ten)
- Pale skin, weakness, breathlessness due to low number of red blood cells or low haemoglobin
- Excessive or prolonged bleeding or bruising due to low number of platelets
- Fever with dangerously low white blood cell count
- Increased risk of infection due to abnormally low number of white blood cells
- Frequent and persistent infections due to decreased antibodies in your blood
- Weakness, abnormal heart rhythms due to abnormally low level of blood salts including phosphorus, potassium
- High levels of liver enzymes or creatinine in the blood that show that your liver or kidneys are not working normally
- Fast or irregular heart rate
- High blood pressure
- Shortness of breath, labored breathing, rapid breathing
- Cough
- Abdominal pain, constipation
- Bone and back pain
- Skin rash
- Swollen ankles, limbs and face

Common side effects (effects that occur in 1-10 in 100 users)
- Fever, malaise, enlarged liver, yellow colour of your skin and eyes, low blood cell counts due to severe immune activation
- Dizziness or fainting, flushing, rash, itching, fever, shortness of breath or vomiting, abdominal pain, diarrhoea due to infusion-related reaction
- Rash, nausea, vomiting, diarrhoea including bloody stools (possible symptoms of graft-versus-host disease, in which transplanted cells attack your cells)
- Pain in the joints due to high level of uric acid
- Abnormal blood test results (high level of: phosphorus, potassium, calcium, sodium, fibrin D-dimer, serum ferritin; low level of: blood protein called albumin, sodium, magnesium)
- Convulsion, fits
- Muscle spasms/cramping due to abnormally low level of blood salts including calcium
- Involuntary or uncontrollable movements
- Involuntary shaking of the body, difficulty writing, difficulty expressing thoughts verbally, impaired attention, sleepiness
- Tingling or numbness, difficulty moving because of nerve damage
- Decreased vision
- Thirst, low urine output, dark urine, dry flushed skin, irritability (possible symptoms of high level of sugar in blood)
- Weight loss
- Nerve pain
- Anxiety, irritability
- Severe state of confusion
- Difficulty sleeping
- Breathlessness, difficulty breathing when lying down, swelling of the feet or legs (possible symptoms of heart failure), stopped heartbeat
- Swelling and pain due to blood clots
- Swelling due to fluids leaking from blood vessels into the surrounding tissue
- Bloating and discomfort (abdominal distension) due to an accumulation of fluid in the abdomen
- Dry mouth, sore mouth, bleeding in the mouth
- Yellow skin and eyes due to abnormally high levels of bilirubin in the blood
- Itching
- Excessive sweating, night sweats
- Flu-like illness
- Failure of multiple organs
- Fluid in the lungs
- Stuffy nose
- Defect in blood clotting (coagulopathy, increased international normalised ratio, prolonged prothrombin time, decreased blood fibrinogen, prolonged activated partial thromboplastin time)

Uncommon side effects (effects that occur in 1-10 in 1,000 users)
- Abnormal blood test results (high level of magnesium)
- Weakness or paralysis of limbs or face, difficulty speaking (possible symptoms of stroke as a result of reduced blood supply)
- Warm or rapidly reddening skin
- Cough that produces phlegm or sometimes blood, fever, shortness of breath or difficulty breathing
- Difficulty in controlling movement

Rare side effects (effects that occur in 1-10 in 10,000 users)
- A new type of cancer beginning in a type of white blood cells called T-cells (secondary malignancy of T-cell origin)

Side effects of unknown frequency (effects whose frequency has not been determined yet)
- Difficulty breathing or dizziness (possible symptoms of an allergic reaction)
- Weakness or numbness in the arms or legs, worsening of or loss of vision, having fixed and irrational thoughts that are not shared by others, headache, impaired memory or thinking, unusual behaviour

If a side effect occurs, if one of the side effects worsens, or if you suffer from a side effect not mentioned in the leaflet, consult with the doctor.

Reporting side effects
Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il
Side effects can also be reported to Novartis company via the email address: safetydesk.israel@novartis.com

5. HOW SHOULD THE MEDICINE BE STORED?

The following information is intended for doctors only.

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 infusion bag label after EXP.

Store ≤ -120°C, in the vapor phase of liquid nitrogen. The product should be administered immediately after thawing. After thawing, the product should be kept at room temperature (20-25°C) and infused within 30 minutes to maintain maximum product viability, including any interruption during the infusion.
Do not use this medicine if the infusion bag is damaged or leaking.

6. FURTHER INFORMATION

What Kymriah contains
- The active substance is tisagenlecleucel. Each infusion bag of Kymriah contains tisagenlecleucel cell dispersion at a batch-dependent concentration of autologous T cells genetically modified to express an anti-CD19 chimeric antigen receptor (CAR-positive viable T cells). 1-3 bags contain a total of 1.2×10⁶ – 6×10⁸ CAR+ viable T cells.
- In addition to the active ingredient, the medicine also contains: Albumin, Dextrose, Dextran 40 for injection, Sodium chloride, Sodium gluconate, Sodium acetate, N-acetyltryptophanate, Sodium, Caprylate, Potassium chloride, Magnesium chloride, DMSO, Aluminium, Dimethyl sulfone, Potassium, 5'-hydroxymethylfurfural, Water for injections.

See section 2 "**Important information about some of the ingredients of the medicine** - Kymriah contains sodium, dimethylsulfoxide (DMSO), dextran 40 and potassium".
This medicine contains cells of human origin.

What the medicine looks like and the contents of the pack:
Kymriah is a cell dispersion for intravenous infusion. The medicine is supplied in an infusion bag containing a colorless to yellowish dispersion.
There are 1-3 50 mL infusion bags, each containing 10-30 mL or 250 mL infusion bags, each containing 30-50 mL.

Registration Holder and Importer and its address: Novartis Israel Ltd., P.O.B. 7126, Tel Aviv.

Revised in April 2025.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 162 91 35711

המידע הבא מיועד לצוות רפואי בלבד:

The following information is intended for healthcare professionals only:

Precautions to be taken before handling or administering the medicinal product
Kymriah should be transported within the facility in closed, break-proof, leak-proof containers.
This medicinal product contains human blood cells. Healthcare professionals handling Kymriah must take appropriate precautions (wearing gloves and eye protection) to avoid potential transmission of infectious diseases.

Preparation prior to administration
Before administration, it must be confirmed that the patient's identity matches the unique patient information on the Kymriah infusion bags and accompanying documentation. The total number of infusion bags to be administered should also be confirmed with the patient specific information on the batch specific documentation accompanying the medicinal product.
The timing of thaw of Kymriah and of infusion should be coordinated. The infusion start time should be confirmed in advance and adjusted for thaw so that Kymriah is available for infusion when the recipient is ready. Once Kymriah has been thawed and is at room temperature (20°C-25°C), it should be infused within 30 minutes to maintain maximum product viability, including any interruption during the infusion.

Inspection and thawing of the infusion bag(s)
Do not thaw the product until it is ready to be used.
The infusion bag should be placed inside a second, sterile bag during thawing to protect ports from contamination and avoid spills in the unlikely event of the bag leaking. Kymriah should be thawed at 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. The bag should be removed immediately from the thawing device and kept at room temperature (20°C-25°C) until infusion (the infusion should be ended within 30 minutes from thawing). If more than one infusion bag has been received for the treatment dose (refer to the batch certificate for number of bags constituting one dose), the next bag should only be thawed after the contents of the preceding bag have been infused.
Kymriah should not be manipulated. For example, Kymriah should not be washed (spun down and resuspended in new media) prior to infusion.
The infusion bag(s) should be examined for any breaks or cracks prior to thawing. If the infusion bag appears to have been damaged or to be leaking, it should not be infused and should be disposed of according to local guidelines on handling of biological waste.

Administration
Kymriah intravenous infusion should be administered by a healthcare professional experienced with immunosuppressed patients and prepared to manage anaphylaxis. In the event of cytokine release syndrome (CRS), ensure that at least one dose of tocilizumab per patient and emergency equipment are available prior to infusion. Hospitals must have access to additional doses of tocilizumab within 8 hours. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the Ministry of Health website, ensure that suitable alternative measures to treat cytokine release syndrome are available on site.
The patient's identity should be matched with the patient identifiers on the infusion bag. Kymriah is intended solely for autologous use and must not, under any circumstances, be administered to other patients. Kymriah should be administered as an intravenous infusion using latex-free intravenous tubing without a leukocyte depleting filter, at approximately 10 to 20 mL per minute by gravity flow. All contents of the infusion bags should be infused. Sterile sodium chloride 9 mg/mL (0.9%) solution for injection should be used to prime the tubing prior to infusion and rinse it after infusion. When the full volume of Kymriah has been infused, the infusion bag should be rinsed with 10 to 30 mL sodium chloride 9 mg/mL (0.9%) solution for injection by back priming to ensure as many cells as possible are infused into the patient.
If the volume of Kymriah to be administered is ≤20 mL, intravenous push may be used as an alternative method of administration

Measures to take in case of accidental exposure
In case of accidental exposure, local guidelines on handling of human-derived material should be followed. Work surfaces and materials which have potentially been in contact with Kymriah must be decontaminated with appropriate disinfectant.

Precautions to be taken for the disposal of the medicinal product
Unused medicinal product and all material that has been in contact with Kymriah (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of human-derived material.