Patient leaflet in accordance with the Pharmacists' (Products) Regulations - 1986
This medicine is to be supplied by doctor's prescription only

YESCARTA®
0.4 – 2 x 10^8 cells dispersion for infusion

Active ingredients:
The active substance is axicabtagene ciloleucel. Each patient-specific single infusion bag contains a dispersion of genetically modified anti-CD19 CAR (chimeric antigen receptor) T cells in approximately 68 mL for a target dose of 2 x 10^6 anti-CD19 CAR-positive viable T cells/kg.

Inactive and allergenic substances: see section 6 *"Additional information*".

Read all of this leaflet carefully before you start taking this medicine. This leaflet contains essential information about this medicine. If you have any further questions, ask your healthcare provider team. This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

In addition to the patient leaflet, the product Yescarta has a patient safety card which contains important safety data that you should be aware of, before receiving Yescarta treatment and following the treatment. You should follow this information. Read the patient safety card and the patient leaflet before treatment initiation. Keep the patient safety card, you may need to read it again.

1. What is the medicine intended for?

Yescarta is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

Limitation of Use: Yescarta is not indicated for the treatment of patients with primary or secondary central nervous system lymphoma.

Therapeutic group: Other antineoplastic agents

Yescarta is a gene therapy medicine used for treating adults with aggressive diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) affecting your lymph tissue (part of the immune system) that affects a type of white blood cell called B lymphocytes and other organs in your body. Too many of these abnormal white blood cells accumulate in your tissue and this is the cause of the symptoms you may have. It is used to treat these conditions when other available medicines have stopped working for you.

The medicine is made specially for you as a single administration of your own modified white blood cells. It is given by a drip (*infusion*) into a vein (*intravenously*).

2. Before the treatment

Do not take this medicine if:
if you are allergic to the active ingredient axicabtagene ciloleucel or to any of the additional ingredients of this medicine (listed in section 6).

Special warnings relating to the use of this medicine

Yescarta is made from your own white blood cells and must only be given to you (*autologous use*).

Before you are given Yescarta you must tell your doctor if you:
- have problems with your nervous system (such as fits, stroke, or memory loss).
- have kidney problems.
- have low blood cell levels (blood counts).
- have had a stem cell transplant in the last 4 months.
- have any lung, heart or blood pressure (low or raised) problems.
- have signs or symptoms of graft-versus-host disease. This happens when transplanted cells attack your body, causing symptoms such as rash, nausea, vomiting, diarrhoea and bloody stools.
- notice the symptoms of your cancer are getting worse. If you have lymphoma this might include fever, feeling weak, night sweats, sudden weight loss.
- have an infection. The infection will be treated before the Yescarta infusion.
- have had hepatitis B, hepatitis C or human immunodeficiency virus (HIV) infection.

If any of the above apply to you (or you are not sure), talk to your doctor before being given Yescarta.

After you have been given Yescarta
Tell your healthcare provider team immediately if you have any of the following:
- Chills, extreme tiredness, weakness, dizziness, headache, cough, shortness of breath, or rapid heartbeat, which may be symptoms of a condition known as cytokine release syndrome. Take your temperature twice a day for 3-4 weeks after treatment with Yescarta. If your temperature is high, see your doctor immediately.
- Fits, shaking, or difficulty speaking or slurred speech (speak (words) indistinctly so that the sounds run into one another), loss of consciousness or decreased level of consciousness, confusion and disorientation, loss of balance or coordination.
- Fever, which may be a symptom of an infection.
- Extreme tiredness, weakness and shortness of breath, which may be symptoms of a lack of red blood cells.
- Bleeding or bruising more easily, which may be symptoms of low levels of cells in the blood known as platelets.

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

Children and adolescents

Yescarta must not be used in children and adolescents below 18 years of age.

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

After Yescarta treatment your doctor will:
- Monitor you for secondary malignancy for your entire life.
- Test your immunoglobulin levels (proteins produced by the immune system).

- Monitor you at the qualified healthcare facility following infusion at least daily for 10 days to check if your treatment is working and help you if you have any side effects. After the first 10 days after infusion you will be monitored at your doctor's discretion.

Drug-drug Interactions

Before Yescarta treatment, tell your healthcare provider team if you are taking or have recently taken any other medicines including non-prescription medicines and dietary supplements.
Especially if you are taking or have recently taken any medicines that weaken your immune system such as corticosteroids, since these medicines may interfere with the effect of Yescarta.

In particular, you must not be given certain vaccines called live vaccines, in the following time periods:
- In the 6 weeks before you are given the short course of chemotherapy (called lymphodepleting chemotherapy) to prepare your body for the Yescarta cells.
- During Yescarta treatment.
- After treatment while the immune system is recovering.

Talk to your doctor if you need to have any vaccinations.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine. This is because the effects of Yescarta in pregnant or breast-feeding women are not known, and it may harm your unborn baby or your breast-fed child. In addition, the effects on male and female fertility have not been evaluated.
- If you are pregnant or think you may be pregnant after treatment with Yescarta, talk to your doctor immediately.
- You will be given a pregnancy test before treatment starts. Yescarta can only be given if the results show you are not pregnant.

Discuss pregnancy with your doctor if you have received Yescarta.

Driving and using machines
Don't drive, use heavy machines or participate in activities that require your alertness. Yescarta has the potential to cause neurologic events, including altered mental status, or seizures during the 8 weeks after the infusion.

Important information regarding the medicine's ingredients
This medicine contains 300 mg sodium (main component of cooking/table salt) in each infusion bag. This is the equivalent to 15% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to take the medicine?

Yescarta will always be given to you by a healthcare professional.
- Since Yescarta is made from your own white blood cells, your cells will be collected from you to prepare your medicine. Your doctor will take some of your blood using a catheter placed in your vein (a procedure call leukapheresis). Some of your white blood cells are separated from your blood and the rest of your blood is returned to your vein. This can take 3 to 6 hours and may need to be repeated.
- Your white blood cells are sent away to make Yescarta. It usually takes about 3 to 4 weeks to receive your Yescarta therapy but the time may vary.

Medicines given before Yescarta treatment
During the 30 to 60 minutes before you are given Yescarta you may be given other medicines. This is to help prevent infusion reactions and fever. These other medicines may include:

- Paracetamol.
- An antihistamine such as diphenhydramine.

Prior to receiving Yescarta, you will be given other medicines such as preparative chemotherapy, which will allow your modified white blood cells in Yescarta to multiply in your body when the medicine is given to you.

Your healthcare provider team will check carefully that this medicine is yours.

How you are given Yescarta

Yescarta will always be given to you by a doctor in a qualified treatment centre.

- Yescarta is given in a single dose.
- Your healthcare provider team will give you a single infusion of Yescarta through a catheter placed into your vein (*intravenous* infusion) over about 30 minutes.
- Yescarta is the genetically modified version of your white blood cells. Your healthcare professional handling the treatment will therefore take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases and will follow local guidelines on handling of waste of human-derived material to clean up or dispose of any material that has been in contact with it.

You must receive Yescarta infusion in a qualified clinical facility and be discharged only when your doctor thinks it is safe for you to go home.
Your doctor may do blood tests to check for side effects.

After you are given Yescarta
- Plan to stay within proximity from the hospital where you were treated for at least 4 weeks after the Yescarta treatment. Your doctor will recommend that you return to the hospital daily for at least 10 days and will consider whether you need to stay at the hospital as an in-patient for the first 10 days after infusion. This is so your doctor can check if your treatment is working and help you if you have any side effects.

If you miss any appointments, call your doctor or the qualified clinical facility as soon as possible to reschedule your appointment.

If you have any further questions on the use of this medicine, consult your healthcare provider team.

4. Side effects

Like all medicines, Yescarta can cause side effects, do not be alarmed by reading the list of side effects. You may not experience any of them.

Yescarta can cause side effects to your immune system that may be serious or life-threatening, and can lead to death.

The following side effects have been reported with Yescarta.

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

- Fever, chills, reduced blood pressure which may cause symptoms such as dizziness, lightheadedness, fluid in the lungs, which may be severe and can be fatal (all symptoms of a condition called *cytokine release syndrome*).
- Abnormally low number of white blood cells.

- Loss of consciousness or decreased level of consciousness, confusion or memory loss due to disturbances of brain function, involuntary shaking (*tremor*), sudden confusion with agitation, disorientation, hallucination or irritability (*delirium*).
- Decrease in the number of red blood cells: symptoms can include extreme tiredness.
- Extreme tiredness.
- Decrease in the number of platelets (*thrombocytopenia*): symptoms can include excessive or prolonged bleeding or bruising.
- Muscle and joint pain, back pain.
- Headache.
- High blood levels of uric acid, or magnesium. Low blood levels of sodium or phosphate.
- Nausea, constipation, diarrhoea, abdominal pain, vomiting.
- Decreased appetite, weight loss.
- Low blood pressure, dizziness.
- Shortness of breath, cough.
- Fast or slow heartbeat.
- Irregular heartbeat (*arrhythmia*).
- Low levels of immunoglobulins.
- Kidney problems causing your body to hold onto fluid, build-up of fluids in tissue (*oedema*) which can lead to weight gain and difficulty in breathing, decreased output of urine.
- Lack of energy or strength, muscular weakness, difficulty moving, muscle spasm.
- Skin rash or skin problems.
- Difficulty sleeping
- High blood pressure.
- Blood clots: symptoms can include pain in the chest or upper back, difficulty breathing, coughing up blood or cramping pain, swelling in a single leg, warm and darkened skin around the painful area.
- Increase in blood level of liver enzymes.

Common side effects (may affect up to 1 in 10 people)
- Dry mouth, dehydration, difficulty swallowing.
- Pain in the hands or feet.
- High blood levels of bilirubin. Low blood levels of albumin, potassium or calcium.
- Low oxygen level in blood.
- Failure of the kidneys.
- Swelling in the limbs, fluid around the lungs (*pleural effusion*).
- Lung infection.
- Alteration of the blood ability to form clots (*coagulopathy*): symptoms can include excessive or prolonged bleeding or bruising
- Changes in vision which makes it difficult to see things (*visual impairment*).
- Pain.
- Sudden, unexpected stopping of the heart (cardiac arrest); this is serious and life-threatening.
- Heart failure.
- Fits (*seizures*).
- Inability to move one side of the body.
- Hypersensitivity: symptoms such as rash, hives, itching, swelling and anaphylaxis.
- Mood disorders.
- Nasal inflammation.
- Weakness or inability to move on one side of the body, making it hard to perform everyday activities like eating or dressing.
- Loss of control of body movements.

Uncommon (may affect up to 1 in 100 people)
- Difficulty understanding numbers, memory loss, fits.
- Breakdown of muscle tissue that leads to the release of muscle fibre into the blood.
- Improper functioning of at least 2 organs (eg, liver, lungs and kidneys) that requires medical treatment and/or procedures to restore normal organ function.

- Inflammation and swelling of spinal cord which may cause partial or total paralysis of limbs and torso.
- Paralysis of all four limbs.
- Condition of severe systemic inflammation.
- Inability to breathe on one's own.

→Tell your healthcare provider team immediately if you get any of the side effects listed above.
Do not try to treat your symptoms with other medicines on your own.

Reporting of side effects
If you get any side effects, talk to your healthcare provider team. This includes any possible side effects not listed in this leaflet.
You can report any side effects to the Ministry of Health by clicking on the link "reporting side effect effects following medical treatment" found on the home page of the Ministry of Health website (www.health.gov.il) which directs you to the online side effects reporting form or by clicking on the link:
https://sideeffects.health.gov.il

Additionally, you can also report any side effects directly to the registration holder via email: DrugSafety.Israel@gilead.com.

By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Yescarta

The following information is intended for doctors only.

Prevent poisoning! Keep this medicine as all other medicines out of the sight and reach of children and/or babies in this way you will prevent poisoning. Do not induce vomiting without a doctor's express instruction.

Do not use this medicine after the expiry date which is stated on the container label and infusion bag.

Storage condition:
Store frozen in vapour phase of liquid nitrogen ≤ -150°C until thawed for use.
Do not refreeze.The stability of Yescarta upon completion of thawing is up to 3 hours at room temperature (20˚C to 25°C). However, Yescarta infusion should begin within 30 minutes of thaw completion and the total Yescarta infusion time should not exceed 30 minutes.

This medicine contains genetically-modified human blood cells. Local guidelines on handling of waste of human-derived material must be followed for unused medicinal products or waste material. As this medicine will be given by qualified healthcare professionals, they are responsible for the correct disposal of the product. These measures will help protect the environment.

6. Additional Information

What Yescarta contains

The active substance is axicabtagene ciloleucel. Each patient-specific single infusion bag contains a dispersion of genetically modified anti-CD19 CAR (chimeric antigen receptor) T cells in approximately 68 mL for a target dose of 2 x 10^6 anti-CD19 CAR-positive viable T cells/kg.
The other ingredients (excipients) are: Cryostor CS10, sodium chloride, human albumin. See section 2 "Important information regarding the medicine's ingredients".

What Yescarta looks like and contents of the pack

Yescarta is a clear to opaque, white to red dispersion for infusion, supplied in an infusion bag individually packed in a metal cassette. A single infusion bag contains approximately 68 mL of cell dispersion.

Manufacturer
Kite Pharma Inc.
2355 Utah Avenue
El Segundo, CA 90245
USA

Registration Holder
Gilead Sciences Israel Ltd.
4 HaHarash Street
Hod Hasharon
4524075
Israel

The following information is intended for healthcare professionals only:

It is important that you read the entire content of this procedure prior to administering Yescarta.

Precautions to be taken before handling or administering the medicinal product

- Yescarta contains genetically-modified human blood cells. Local guidelines on handling of waste of human-derived material applicable for such products must be followed.
- Yescarta must be transported within the facility in closed, break-proof, leak-proof containers.
- Yescarta is prepared from autologous blood of the patient collected by leukapheresis. Patient leukapheresis material and Yescarta may carry a risk of transmitting infectious viruses to healthcare professionals (HCP) handling the product. Accordingly, HCP must employ appropriate precautions (wearing gloves and glasses) when handling leukapheresis material or Yescarta to avoid potential transmission of infectious diseases.
- Work surfaces and materials that have potentially been in contact with Yescarta must be decontaminated according to local guidelines on the handling of waste of human-derived materials.

Preparation for infusion

- Verify that the patient's identity (ID) matches the patient identifiers on the Yescarta cassette.
- The Yescarta product bag must not be removed from the metal cassette if the information on the patient-specific label does not match the intended patient.
- Once the patient's ID is confirmed, remove the Yescarta product bag from the metal cassette.
- Check that the patient information on the metal cassette label matches that on the bag label.
- Inspect the product bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines for handling of waste of human-derived material (or immediately contact Kite).
- Place the infusion bag inside a second bag.
- Thaw Yescarta at approximately 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Yescarta must not be washed, spun down, and/or re-suspended in new medium prior to infusion. Thawing takes approximately 3 to 5 minutes.
- Once thawed, Yescarta is stable at room temperature (20˚C-25˚C) for up to 3 hours. However, Yescarta infusion must begin within 30 minutes of thaw completion.

Do NOT use a leukodepleting filter.

Administration
- The medicine must be administered in a qualified treatment centre by a physician(s) with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with Yescarta.
- Ensure that at least 1 dose of tocilizumab per patient and emergency equipment are available prior to infusion and during the recovery period. Hospitals should have access to an additional dose of tocilizumab within 8 hours of each previous dose.
- The patient's identity must be matched with the patient identifiers on the infusion bag.
- Yescarta is for autologous use only.
- Yescarta must be administered as an intravenous infusion using latex-free intravenous tubing without a leukocyte depleting filter within 30 minutes by either gravity or a peristaltic pump.
- Gently agitate the bag during Yescarta infusion to prevent cell clumping. All contents of the infusion bags must be infused.
- Sterile sodium chloride 9 mg/mL (0.9%) (0.154 mmol sodium per mL) solution for injection must be used to prime the tubing prior to infusion as well as rinse it afterwards. When the full volume of Yescarta has been infused, the infusion bag must 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.

Disposal of Yescarta
- Any unused medicinal product or waste material that has been in contact with Yescarta (solid and liquid waste) must be handled and disposed in accordance with local guidelines on the handling of waste of human-derived material. Work surfaces and material which have potentially been in contact with Yescarta must be decontaminated with appropriate disinfectant.

Accidental exposure
- Accidental exposure to Yescarta must be avoided. Local guidelines on handling of waste of human derived-material must be followed in case of accidental exposure, which may include washing of the contaminated skin, and removal of contaminated clothes.

The medicine's registration no. in the national register of medicines at the Ministry of Health: 35695

For simplicity and ease of reading, this leaflet was phrased in the masculine. Nevertheless, the medicine is intended for both sexes.

Revised in July 2022 according to MOHs guidelines.
Reference: EU PIL from June 2022

IL-JUL22-EU-JUN22