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

This medicine is dispensed with a doctor's prescription only

Breyanzi®

Dispersion for intravenous infusion

Active ingredient

lisocabtagene maraleucel

1.1-70 x 10^6 chimeric antigen receptor [CAR] positive viable T cells/mL / 1.1-70 x 10^6 chimeric antigen receptor [CAR] positive viable T cells/mL (CD8+ cell component and CD4+ cell component)

Inactive ingredients and allergens in the medicine: 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, consult your doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.

Patient Card

In addition to the leaflet, Breyanzi also has a patient card.

This card contains important safety information that you need to know before starting and during treatment with Breyanzi and which you should follow. Carefully read the patient card and patient leaflet before you start using this medicine. Keep the card in case you need to read it again.

1. What is this medicine intended for?

- Breyanzi is indicated for the treatment of adult patients with large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B) who have:
  - refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or
  - refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age.
- Breyanzi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B) after two or more lines of systemic therapy.

Therapeutic group: Other antineoplastic agents.

Breyanzi contains the active substance lisocabtagene maraleucel, a type of treatment called 'genetically modified cell therapy'.

Breyanzi is made from your own white blood cells. This involves blood filtration - separating the white blood cells and sending them to a laboratory so that they can be modified to make Breyanzi.

How Breyanzi works

- Breyanzi cells have been genetically modified to recognise the lymphoma cells in your body.
- When these cells are introduced back into your blood, they can recognise and attack the lymphoma cells.

2. Before using this medicine

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient or to any of the ingredients in this medicine (see section 6). If you think you may be allergic, ask your doctor for advice.
- You cannot receive treatment called lymphodepleting chemotherapy, which reduces the number of white blood cells in your blood (see also section 3 'How to use this medicine').

Special warnings about using this medicine

Before treatment with Breyanzi, tell your doctor if:

- You have any lung or heart problems
- You have low blood pressure
- You have an infection or other inflammatory conditions. The infection will be treated before you are given Breyanzi
- You have had a stem cell transplant from another person in the last 4 months – the transplanted cells can attack your body (graft-versus-host disease), causing symptoms such as rash, nausea, vomiting, diarrhoea and bloody stools
- You notice that the symptoms of your cancer are getting worse. These symptoms include fever, feeling weak, night sweats, sudden weight loss
- You have had hepatitis B or C, or human immunodeficiency (HIV) infection
- You had a vaccination in the last 6 weeks or you are planning to have one in the next few months. See **'Live vaccines'** below for more information.

If you think that any of the above apply to you (or you are not sure), talk to your doctor before receiving Breyanzi.

Patients treated with Breyanzi may develop new types of cancers. There have been reports of patients developing cancer, originating in a type of white blood cells called T-cells, after treatment with Breyanzi 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.

Children and adolescents

Breyanzi is not indicated for children and adolescents below 18 years of age. There is no information about the safety and efficacy of using this medicine in children and adolescents.

Tests and follow-up

Before you are given Breyanzi, your doctor will:

- check your lungs, heart and blood pressure.
- look for signs of infection – any infection will be treated before you receive Breyanzi.
- look for signs of graft-versus-host disease, which may happen after a stem cell transplant from another person.
- check your blood for uric acid and for how many cancer cells there are in your blood. These 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 if your cancer is getting worse.
- check for hepatitis B and C, and HIV infection.

After you have been given Breyanzi

- If you get certain serious side effects, you must tell your doctor or nurse straight away because you may need treatment for them. See section 4 under 'Serious side effects'.
- Your doctor will regularly check your blood counts, as the number of blood cells may decrease.
- Stay close to the treatment centre where you had received Breyanzi for at least 4 weeks. See sections 3 and 4.
- Do not donate blood, organs, tissues or cells for transplantation.

You will be asked to enrol in a registry for at least 15 years in order to better understand the long-term effects of Breyanzi.

Interactions with other medicines

If you are taking or have recently taken other medicines, including nonprescription medicines and dietary supplements, tell your doctor or pharmacist.

See section 3 for information about the medicines you will be given before receiving Breyanzi.

Medicines that affect your immune system

Before you are given Breyanzi, tell your doctor or nurse if you are taking any medicines that weaken your immune system, such as:

- corticosteroids.

This is because these medicines may reduce the effect of Breyanzi.

Other medicines that treat cancer

Some anti-cancer medicines could reduce the effect of Breyanzi. Your doctor will consider if you need other cancer treatments.

Live vaccines

You must not be given certain vaccines called live vaccines:

- in the 6 weeks before you are given the short course of chemotherapy (called lymphodepleting chemotherapy) to prepare your body for Breyanzi.
- during Breyanzi treatment.
- after treatment, while your immune system is recovering.

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

Pregnancy, breastfeeding and fertility

If you are pregnant or breastfeeding, think you may be pregnant or are planning to become pregnant, ask your doctor for advice before receiving this medicine or lymphodepleting chemotherapy. The effects of Breyanzi in pregnant or breast-feeding women are not known, and it may harm your unborn baby or breast-fed child.

- If you are pregnant or think you may be pregnant after treatment with Breyanzi, talk to your doctor immediately.
- You will undergo a pregnancy test before treatment starts. Breyanzi should only be given if the result shows that you are not pregnant.

Discuss the need for contraception with your doctor.

Discuss pregnancy with your doctor if you have received Breyanzi.

The doctor will consider testing immunoglobulin and B cell levels in babies of mothers treated with Breyanzi.

Driving and using machines

Do not drive, use machines, or take part in activities that need you to be alert for at least 8 weeks after treatment. Breyanzi may make you sleepy, decrease awareness, and cause confusion and seizures (fits).

Important information about some of this medicine's ingredients

Breyanzi contains sodium, potassium and dimethyl sulfoxide (DMSO)

This medicine contains up to 12.5 mg sodium (main component of cooking/table salt) per vial. This is equivalent to 0.6% of the recommended maximum daily intake of sodium for an adult. Up to 8 vials of this medicine may be given per dose, which in total contain 100 mg sodium or 5% of the recommended maximum daily intake of sodium for an adult.

This medicine contains up to 0.2 mmol (or 6.5 mg) potassium per dose. Your doctor will take this potassium content into consideration if your kidneys do not work properly or if you are on a controlled potassium diet.

This medicine also contains dimethyl sulfoxide, which may cause severe hypersensitivity reactions.

3. How to use this medicine?

Always use this medicine according to your doctor's instructions. Check with your 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 how you should take this medicine.

Patient Card

- Your doctor will give you a Patient Card. Read it carefully and follow the instructions on it.
- Always show the Patient Card to the doctor or nurse when you see them or if you go to a hospital.

Collecting blood to make Breyanzi from your white blood cells

Breyanzi is made from your own white blood cells.

- Your doctor will take blood from you by inserting a tube (catheter) into your vein. Some of your white blood cells will be separated from your blood. The rest of your blood will be returned to your body. This is called leukapheresis and may take 3 to 6 hours. This process may need to be repeated.
- Your white blood cells will then be sent to make Breyanzi.

Other medicines you will be given before Breyanzi

- A few days before you receive Breyanzi, you will be given a short course of chemotherapy. This is to clear away your existing white blood cells.
- Shortly before you receive Breyanzi, you will be given paracetamol and an antihistamine medicine. This is to reduce the risk of infusion reactions and fever.

How Breyanzi is given

- Your doctor will verify that the Breyanzi was prepared from your own blood by checking that the patient identity information on the medicine labels matches your details.
- Breyanzi is given by infusion (drip) through a tube into a vein.
- You will receive infusions of the CD8 positive cells, followed immediately by infusions of the CD4 positive cells. The time for infusion will vary, but will usually be less than 15 minutes for each of the 2 cell types.

After Breyanzi is given

- Stay close to the treatment centre where you received Breyanzi for at least 4 weeks.
- During the first week after treatment, you will be monitored at the treatment centre 2 to 3 times so that your doctor can check that the treatment is working and help you cope with any side effects. See sections 2 and 4.

If you miss an appointment

Call your doctor or the medical centre as soon as possible to make another appointment.

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 about using this medicine, consult your doctor or pharmacist.

4. Side effects

As with any medicine, using Breyanzi may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

Serious side effects

Tell your doctor immediately if you get any of the following side effects after receiving Breyanzi:

- fever, chills or shaking, feeling tired, fast or uneven heartbeat, feeling light-headed and short of breath – these may be signs of a serious problem called cytokine release syndrome.
- confusion, being less alert (decreased consciousness), difficulty speaking or slurred speech, shaking (tremour), feeling anxious, feeling dizzy and headache – these may be symptoms of neurological toxicity called immune effector cell-associated neurotoxicity syndrome (ICANS), or signs of problems with your nervous system.
- feeling warm, fever, chills or shivering – these may be signs of infection. The infections may be caused by:
  - low levels of white blood cells, which help fight infections, or
  - low levels of antibodies called immunoglobulins
- blurred vision, loss of vision or double vision, difficulty speaking, weakness or clumsiness of an arm or a leg, a change in the way you walk or problems with your balance, personality changes, changes in thinking, memory and orientation leading to confusion. These may all be symptoms of a serious and potentially fatal brain condition called progressive multifocal leukoencephalopathy (PML). These symptoms may start several months after treatment has ended and they usually develop slowly and gradually over weeks or months. It is important that your relatives or caregivers are also aware of these symptoms, since they may notice symptoms that you are not aware of.
- feeling very tired, weak and short of breath – these may be signs of low red blood cell levels (anaemia).
- bleeding or bruising more easily – these may be signs of low levels of blood cells known as platelets.

Tell your doctor immediately if you get any of the above side effects after receiving Breyanzi, as you may need urgent medical treatment.

Additional side effects

Very common side effects - affect more than one in ten users:

- difficulty sleeping
- low blood pressure including signs such as dizziness, passing out or change in eyesight
- cough
- feeling sick or being sick
- diarrhoea or constipation
- stomach pain
- swollen ankles, arms, legs and face
- rash.

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

- trouble with balancing or walking
- high blood pressure which may include signs of very severe headaches, sweating or trouble sleeping
- changes in vision
- changes in the way things taste
- numbness and tingling in the feet or hands
- blood clots or problems with blood clotting
- bleeding in your gut
- passing less urine
- infusion reactions – such as feeling dizzy, fever, and shortness of breath
- low blood levels of phosphates
- low levels of oxygen in the blood.

Uncommon side effects - affect 1–10 in 1000 users:

- a new type of cancer originating in a type of white blood cells called T-cells (secondary malignancy of T-cell origin)
- fast breakdown of cancer cells, resulting in the release of toxic waste products into the bloodstream – a sign may be dark urine with symptoms of nausea or pain on a side of the stomach
- severe inflammatory condition – symptoms may include fever, rash, enlarged liver, spleen and lymph nodes
- heart weakness, causing shortness of breath and ankle swelling
- fluid around the lungs
- stroke or mini-strokes
- convulsions or seizures (fits)
- weakness of the face muscles, vocal cords or weakness in the body
- swelling of the brain.

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 'Reporting Side Effects of Drug Treatment' link on the Ministry of Health home page (www.health.gov.il), which opens an online form for reporting side effects, or 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) which is stated on the vial labels and cartons. The expiry date refers to the last day of that month.

Storage conditions: Store frozen in the vapour phase of liquid nitrogen (≤ -130°C). The product should be administered immediately after thawing.

After thawing, the product can be used for up to 2 hours at room temperature (15°C - 25°C). Do not refreeze.

6. Additional information

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

Cryostor CS10 (contains 10% dimethyl sulfoxide (DMSO)), plasma protein (human albumin), sodium chloride, sodium gluconate, sodium acetate trihydrate, potassium chloride, magnesium chloride, N-acetyl-DL-tryptophan, caprylic acid, water for injection.

What the medicine looks like and contents of the pack:

Breyanzi is a cell dispersion for infusion. It is supplied in vials containing slightly opaque to opaque, colourless to yellow, or brownish-yellowish dispersion.

Each 4.6 mL vial contains a dispersion of CAR-positive viable T cells (CD8 positive cell component or CD4 positive cell component) at the concentration of 1.1 x 10^6 to 70 x 10^6 CAR-positive viable T cells/mL for each cell component. There may be up to 4 vials of each of the CD8 positive or CD4 positive cell components, depending on the concentration of cryopreserved medicine.

Registration holder's name and address: Bristol-Myers Squibb (Israel) Ltd., 18 Aharon Bart St. P.O.B. 3361, Kiryat Arye, Petach Tikva 4951448.

Manufacturer's name and address:

Bristol-Myers Squibb Ltd, Route 206 & Province Line Road, Princeton, New Jersey 08543, USA

Revised in June 2025

Registration number of the medicine in the Ministry of Health National Drug Registry: 179-13-38093

המידע שלהלן מיועד לאנשי צוות רפואי בלבד:

المعلومات التالية مخصصة لأفراد الطاقم الطبي فقط:

The following information is intended for healthcare professionals only:

Precautions to be taken before handling or administering the medicinal product

Breyanzi must be transported within the treatment centre in closed, break-proof, leak-proof containers.

This medicinal product contains human blood cells. Healthcare professionals handling Breyanzi should take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.

Preparation prior to administration

***Before** thawing the vials*

- Confirm the patient's identity with the patient identifiers on the shipper.
- Breyanzi is composed of CAR-positive viable T cells formulated as separate CD8+ and CD4+ cell components; there is a separate release for infusion certificate (RfIC) for each cell component. Read the RfIC (affixed inside the shipper) for information on the number of syringes you will need and the volume to be administered of the CD8+ and CD4+ cell components (syringe labels are provided with the RfIC).
- Confirm the infusion time in advance and adjust the start time of Breyanzi thaw such that it will be available for infusion when the patient is ready.

  Note: Once the vials of CAR-positive viable T cells (CD8+ and CD4+ cell components) are removed from frozen storage, the thaw must be carried to completion and the cells administered within 2 hours.

Thawing the vials

- Confirm the patient's identity with the patient identifiers on the outer carton and the release for infusion certificate (RfIC).
- Remove the CD8+ cell component carton and CD4+ cell component carton from the outer carton.
- Open each inner carton and visually inspect the vial(s) for damage. If the vials are damaged, contact the company.
- Carefully remove the vials from the cartons, place vials on a protective barrier pad, and thaw at room temperature. Thaw all vials at the same time. **Take care to keep the CD8+ and CD4+ cell components separate.**

Dose preparation

- Based on the concentration of CAR-positive viable T cells for each component, more than one vial of each of the CD8+ and CD4+ cell components may be required to complete a dose. A separate syringe should be prepared for each CD8+ or CD4+ cell component vial received.

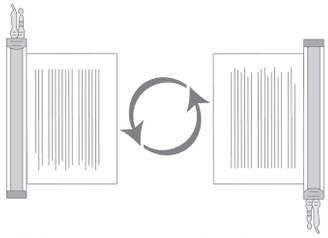
  Note: The volume to be drawn up and infused may differ for each component.

- Each 5 mL vial contains a total extractable volume of 4.6 mL of CD8+ or CD4+ cell component T cells. The RFI Certificate for each component indicates the volume (mL) of cells to be drawn up into each syringe. Use the smallest Luer-lock tip syringe necessary (1 mL to 5 mL) to draw up the specified volume from each vial. A 5 mL syringe should not be used for volumes less than 3 mL.
- **Prepare the syringe(s) of the CD8+ cell component first.** Confirm that the patient identifiers on the CD8+ cell component syringe label match the patient identifiers on the CD8+ cell component vial label. Affix the CD8+ cell component syringe labels to the syringe(s) prior to pulling the required volume into the syringe(s).
- Repeat the process for the CD4+ cell component.

  Note: It is important to confirm that the volume drawn up for each cell component matches the volume specified in the respective release for infusion certificate (RfIC).

Withdrawal of the required volume of cells from each vial into a separate syringe should be carried out using the following instructions:

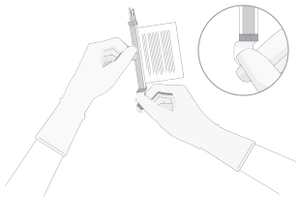
1. Hold the thawed vial(s) upright and gently invert the vial(s) to mix the cell product. If any clumping is apparent, continue to invert the vial(s) until clumps have dispersed and cells appear to be evenly resuspended.



Vial upright Vial inverted

2. Visually inspect the thawed vial(s) for damage or leaks. Do not use if the vial is damaged or if the clumps do not disperse; contact the company. The liquid in the vials should be slightly opaque to opaque, colourless to yellow, or brownish-yellow.
3. Remove the polyaluminium cover (if present) from the bottom of the vial and swab the septum with an alcohol wipe. Allow to air dry before proceeding.

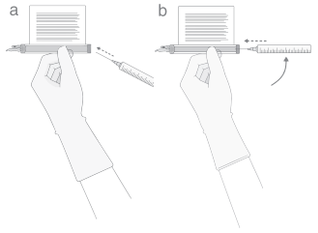
   NOTE: The absence of the polyaluminium cover does not impact the sterility of the vial.



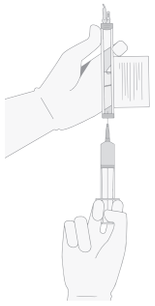
4. Keeping the vial(s) upright, cut the seal on the tubing line on the top of the vial immediately above the filter to open the air vent on the vial.

   NOTE: Be careful to select the correct tubing line with the filter. Cut ONLY the tubing with a filter.

5. Hold a 20 gauge, 1–1 ½ inch needle, with the opening of the needle tip away from the retrieval port septum.
   a. Insert the needle into the septum at a 45 °–60 ° angle to puncture the retrieval port septum.
   b. Increase the angle of the needle gradually as the needle enters the vial.



6. WITHOUT drawing air into the syringe, slowly withdraw the target volume (as specified in the release for infusion certificate [RfIC]).



7. Carefully inspect the syringe for signs of debris prior to proceeding. If there is debris, contact the company.
8. Verify that the volume of CD8+/CD4+ cell component matches the volume specified for the relevant component in the release for infusion certificate (RfIC).

   Once the volume is verified, shift the vial and syringe to a horizontal position, and remove the syringe/needle from the vial.

   Carefully detach the needle from the syringe and cap the syringe.

9. Continue to keep the vial horizontal and return it to the carton to avoid leaking from the vial.
10. Dispose of any unused portion of Breyanzi.

Administration

- **Do NOT** use a leukodepleting filter.
- Ensure tocilizumab and emergency equipment are available prior to infusion and during the recovery period. In the exceptional case where tocilizumab is not available, ensure that suitable alternative measures to treat CRS instead of tocilizumab are available on-site.
- Confirm the patient's identity matches the patient identifiers on the syringe label supplied on the respective RFI certificate.
- Once Breyanzi has been drawn into syringes, proceed with administration as soon as possible. The total time from removal of Breyanzi from frozen storage to patient administration should not exceed 2 hours.
- Use intravenous sodium chloride 9 mg/mL (0.9%) solution for injection to flush all the infusion tubing prior to and after each CD8+ or CD4+ cell component administration.
- Administer the CD8+ cell component first. The entire volume of the CD8+ cell component is administered intravenously at an infusion rate of approximately 0.5 mL/minute, using the closest port or Y-arm (piggyback).
- If more than one syringe is required for a full dose of the CD8+ cell component, administer the volume in each syringe consecutively without any time between administering the contents of the syringes (unless there is a clinical reason to hold the dose, e.g. infusion reaction). After the CD8+ cell component has been administered, flush the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection.
- Administer the CD4+ cell component immediately after administration of the CD8+ cell component is complete, using the same steps and infusion rate described for the CD8+ cell component. Following administration of the CD4+ cell component, flush the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection, using enough flush to clear the tubing and the length of the IV catheter. The time for infusion will vary and will usually be less than 15 minutes for each component.

Measures to take in case of accidental exposure

In case of accidental exposure local guidelines on handling of human derived materials must be followed. Work surfaces and materials which have potentially been in contact with Breyanzi 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 Breyanzi (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling human-derived material.