BREYANZI®

LISOCABTAGENE MARALEUCEL

PRODUCT HANDLING AND ADMINISTRATION GUIDE

Bristol Myers Squibb®

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LIST OF ABBREVIATIONS

CAR	Chimeric antigen receptor
CD	Cluster of differentiation
HCP	Healthcare professional
RfIC	Release for infusion certificate

1. INTRODUCTION

This Guide provides information for handling, thawing, preparation and administration of Breyanzi to minimise the potential risk of reduced viability of Breyanzi due to inappropriate product handling. Please see the Israeli Prescribing Information for full information on handling and administration of Breyanzi.

Breyanzi (lisocabtagene maraleucel) is a cluster of differentiation (CD)19-directed genetically modified autologous cell-based product consisting of purified CD8+ and CD4+ T cells, in a defined composition, that have been separately transduced *ex vivo* using a replication-incompetent lentiviral vector expressing an anti-CD19 chimeric antigen receptor (CAR). Breyanzi is intended for autologous use only via intravenous infusion.

For further information on Breyanzi, including authorised indications, please refer to the Israeli Prescribing Information.

2. PRECAUTIONS TO TAKE BEFORE HANDLING OR ADMINISTERING BREYANZI

Breyanzi must be stored and transported frozen in the vapour phase of liquid nitrogen (≤ –130°C) and must remain frozen until the patient is ready for treatment to ensure viable cells are available for patient administration. Do not refreeze after thawing.

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

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

Breyanzi is intended solely for autologous use and should under no circumstances be administered to other patients. Breyanzi must not be administered if the patient identifiers on the cartons, vials and release for infusion certificate (RfIC) do not match the intended patient, and the company must be contacted immediately.

3. PREPARATION PRIOR TO ADMINISTRATION

Before *thawing the vials:*

- Confirm that the patient's identity matches the patient identifiers on the shipper.
- The vials **must not** be removed from the cartons if the information on the patient-specific label does not match the intended patient.
  The company must be contacted immediately if there are **any** discrepancies between the labels, the RfIC and the patient identifiers.
- Breyanzi is composed of CAR+ viable T cells formulated as separate CD8+ and CD4+ cell components; there is a separate 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+ 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 RfIC.
- Remove the CD8+ cell component carton and CD4+ cell component carton from the outer carton.

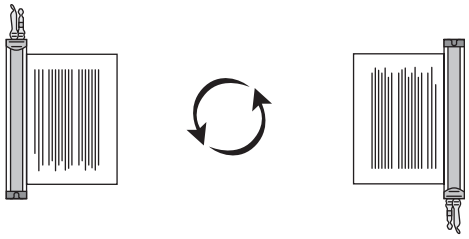
- Open each inner carton and visually inspect the vial(s) for damage. If the vials are damaged, contact the company.
- Carefully remove the vials from the cartons, place vials on a protective barrier pad, and thaw at room temperature. Thaw all vials at the same time.
  Take care to keep the CD8+ and CD4+ cell components separate.

Dose preparation:

- Based on the concentration of CAR+ 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 RfIC 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 RfIC.

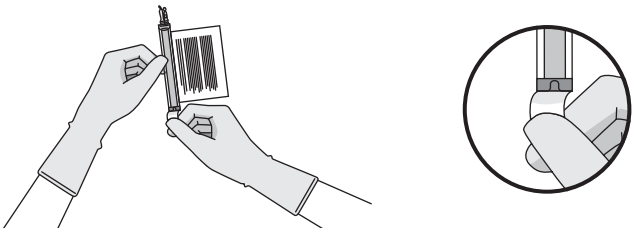
Withdrawal of the required volume of cells from each vial into a separate syringe should be carried out using the following instructions:

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.

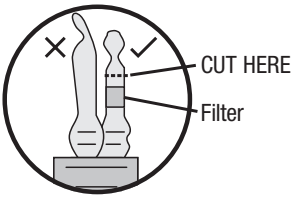


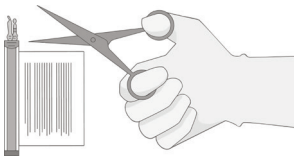
2. Visually inspect the thawed vial(s) for damage or leaks. Do not use if the vial is damaged or if the clumps do not disperse; contact the company. The liquid in the vials should be slightly opaque to opaque, colourless to yellow, or brownish yellow.

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.



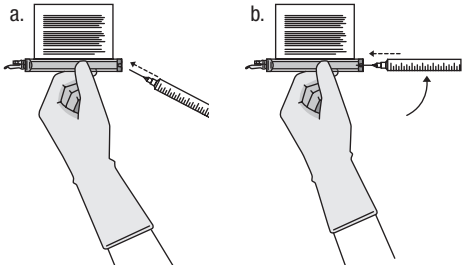
4. Keeping the vial(s) upright, cut the seal on the tubing line on the top of the vial immediately above the filter to open the air vent on the vial.
   NOTE: Be careful to select the correct tubing line with the filter. Cut ONLY the tubing with a filter.





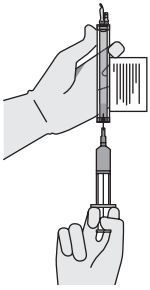
5. Hold a 20 gauge, 1 inch to 1½ inch needle, with the opening of the needle tip away from the retrieval port septum.

   a) Insert the needle into the septum at a 45° to 60° angle to puncture the retrieval port septum.
   b) Increase the angle of the needle gradually as the needle enters the vial.

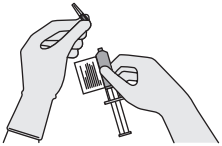
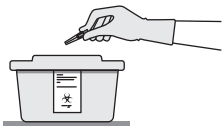
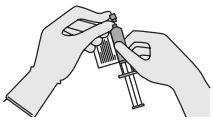


6. WITHOUT drawing air into the syringe, slowly withdraw the target volume (as specified in the RfIC).

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 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.

4. HOW TO ADMINISTER BREYANZI

- **Do NOT** use a leukodepleting filter.
- Ensure tocilizumab or suitable alternatives, in the exceptional case where tocilizumab is not available, and emergency equipment are available prior to infusion and during the recovery period.
- Confirm the patient's identity matches the patient identifiers on the syringe label supplied on the respective RfIC.
- Once Breyanzi has been drawn into the syringes, proceed with administration as soon as possible. The total time from removal 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, eg, 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 intravenous catheter.

The time for infusion will vary and will usually be less than 15 minutes for each component.

5. DISPOSAL AND ACCIDENTAL EXPOSURE

- Unused medicinal products 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.
- In case of accidental exposure, local guidelines on handling of human derived materials should be followed. Work surfaces and materials which have potentially been in contact with Breyanzi must be decontaminated with appropriate disinfectant.

6. COMPANY CONTACT DETAILS

For information on HCP educational material, Israeli Prescribing Information, and patient information, or if you have any questions, please contact BMS by phone: 03 5231021, Fax: 03-9226896 or email: Office_IL@bms.com.

7. REPORTING ADVERSE REACTIONS

Reporting adverse reactions after administration of Breyanzi is important and allows continued monitoring of the benefit-risk balance of the therapy.
Healthcare professionals are asked to adequately and appropriately report adverse reactions that have occurred during the use of Breyanzi.
Adverse reactions may be reported to the Ministry of Health by means of the online form for reporting adverse reactions located on the homepage of the Ministry of Health's website (www.health.gov.il)
or by logging in to https://sideeffects.health.gov.il

You may also report side effects to BMS by phone:
1809-388054 (a toll-free number)
or email MedInfo.Israel@bms.com

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This administration guide and its content have been approved by the Ministry of Health in June 2025 2009-IL-2500005