BREYANZI®

LISOCABTAGENE MARALEUCEL

HEALTHCARE PROFESSIONAL GUIDE

2009-IL-2500007 This Healthcare Professional Guide and its content have been approved by the Ministry of Health in June 2025

Bristol Myers Squibb®

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ASTCT	American Society for Transplantation and Cellular Therapy
CAR	chimeric antigen receptor
CD	cluster of differentiation
CTCAE	Common Terminology Criteria for Adverse Events
CRS	cytokine release syndrome
EBMT	European Society for Blood and Marrow Transplantation
EEG	electroencephalogram
FiO_2	fraction of inspired oxygen
HCP	healthcare professional
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy
ICP	intracranial pressure
IV	intravenously
mAb	monoclonal antibody
scFv	single chain variable fragment

1. INTRODUCTION

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, that have been separately transduced *ex vivo* using a replication-incompetent lentiviral vector expressing an anti-CD19 chimeric antigen receptor (CAR) comprising a single chain variable fragment (scFv) binding domain derived from a murine CD19-specific monoclonal antibody (mAb; FMC63) and a portion of the 4-1BB co-stimulatory endodomain and CD3 zeta (ζ) chain signalling domains and a nonfunctional truncated epidermal growth factor receptor.

Breyanzi contains CAR-positive viable T cells, consisting of a defined composition of CD8+ and CD4+ cell components.
Each 4.6 mL component vial contains lisocabtagene maraleucel at a batch-specific concentration of autologous T cells genetically modified to express anti-CD19 CAR-positive viable T cells.
The medicinal product is packaged in one or more vials containing a cell dispersion of 5.1 to 322 × 10^6 CAR-positive viable T cells (1.1 to 70 × 10^6 CAR-positive viable T cells/mL) for each component suspended in a cryopreservative solution.

Breyanzi is approved in selected indications as specified in the Israeli Prescribing Information.

2. ADDITIONAL RISK MINIMISATION MEASURES

This educational guide is part of the additional risk minimisation measures for Breyanzi and contains information regarding selected Breyanzi-associated adverse reactions of cytokine release syndrome (CRS), neurologic toxicities including immune effector cell-associated neurotoxicity syndrome (ICANS), and secondary malignancy of T-cell origin. These are not all the adverse reactions associated with Breyanzi. Please refer to the Israeli Prescribing Information for more information.

Hospitals and their associated centres are only able to dispense Breyanzi if they are qualified in accordance with the agreed controlled distribution programme by:

- Ensuring immediate on-site access to one dose of tocilizumab per patient prior to Breyanzi infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available, ensuring that suitable alternative measures to treat CRS instead of tocilizumab are available on site.
- Healthcare professionals (HCPs) involved in the treatment of a patient have completed the educational programme.
- Healthcare professionals that are expected to prescribe, dispense and administer Breyanzi to a patient must complete the educational programme by being provided with information in accordance with the agreed HCP Educational Programme.

Detailed instructions on the handling and thawing process for Breyanzi are provided in the Product Handling and Administration Guide.

3. IMPORTANT POINTS TO CONSIDER BEFORE ADMINISTERING BREYANZI

To mitigate the safety risks associated with Breyanzi treatment, CAR T treatment centres must comply with the risk minimisation measures, as outlined in this HCP guide, prior to ordering Breyanzi.

Breyanzi must be administered in a qualified treatment centre.

Hospitals and associated centres must ensure that one dose of tocilizumab (for use in the event of CRS) must be available for immediate on-site use prior to infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion.

Breyanzi therapy should be initiated under the direction of and supervised by an HCP experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with Breyanzi.

The treatment centre is responsible for ensuring that this guide, the Product Handling and Administration Guide and the Patient card are provided to all relevant personnel.

Due to the risks associated with Breyanzi treatment, infusion should be delayed if patients have any of the following conditions:

- Unresolved serious adverse events (especially pulmonary events, cardiac events, or hypotension), including those after preceding chemotherapies.
- Active uncontrolled infections, or inflammatory disorders.
- Active graft-versus-host disease.

4. PATIENT MONITORING FOLLOWING BREYANZI ADMINISTRATION

Patients should be monitored 2 to 3 times during the first week following infusion, for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation at the first signs or symptoms of CRS and/or neurologic events.

Frequency of monitoring after the first week should be carried out at the physician's discretion and continued for at least 4 weeks following infusion.

Patients should be instructed to remain within proximity of the qualified treatment centre for at least 4 weeks following infusion.

Patients should be counselled to seek immediate medical attention should signs and symptoms of CRS and/or neurologic toxicity occur at any time and treated promptly.

Patients should be monitored life-long for secondary malignancies.

The European Society for Blood and Marrow Transplantation (EBMT) is maintaining a registry for follow-up of patients who received Breyanzi. Healthcare professionals should inform their patients about the importance of contributing to such a registry and should encourage their patients to enrol into the registry conducted by EBMT through their treating physician, following Breyanzi treatment for long-term follow-up of safety and efficacy, for up to 15 years post infusion.

5. SAFETY RISKS ASSOCIATED WITH BREYANZI

Cytokine release syndrome, including fatal or life-threatening reactions, can occur following the infusion. At the first sign of CRS, treatment with supportive care, tocilizumab or tocilizumab and corticosteroids should be instituted as described in Table 1.

Neurologic toxicities, including ICANS, which may be fatal or life threatening, have occurred following treatment with Breyanzi, including concurrently with CRS, after CRS resolution, or in the absence of CRS. If neurologic toxicity is suspected, it is to be managed according to the recommendations in Table 2.

Breyanzi continues to expand following administration of tocilizumab and corticosteroids.

Secondary malignancies of T-cell origin, including chimeric antigen receptor (CAR)-positive malignancies, have been reported within weeks and up to several years following treatment of haematological malignancies with a CD19-directed CAR T-cell therapy. There have been fatal outcomes. Patients should be monitored life-long for secondary malignancies.

6. CYTOKINE RELEASE SYNDROME

6.1 Signs and Symptoms of Cytokine Release Syndrome

Cytokine release syndrome is a non-antigen specific toxicity that occurs as a result of high-level immune activation due to the mechanism of action of Breyanzi[1].

Clinical symptoms and severity of CRS are highly variable, ranging from mild flu-like symptoms to multiorgan failure. Fever is a hallmark of CRS.

Management can be complicated by concurrent conditions.

For severe or life-threatening CRS, intensive care unit level monitoring and supportive therapy should be considered.

In clinical studies, the most common manifestations of CRS for patients who receive Breyanzi included pyrexia, hypotension, tachycardia, chills, hypoxia, headache, and fatigue. Refer to the Israeli Prescribing Information Section 4.4. (Special warnings and

precautions for use) and Section 4.8 (Undesirable effects) for a more complete description of the presentation of CRS in the Breyanzi clinical trials.

6.2 Management of Cytokine Release Syndrome

- Patients should be monitored for signs and symptoms of CRS 2 to 3 times during the first week following infusion. Frequency of monitoring after the first week should be carried out at the physician's discretion and continued for at least 4 weeks following infusion.
- Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time.
- Identify CRS based on clinical presentation. Evaluate and treat other causes of fever, hypoxia and hypotension. Haemophagocytic lymphohistiocytosis/macrophage activation syndrome should be considered in patients with severe or unresponsive CRS.
- At the first sign of CRS, treatment with supportive care, tocilizumab or tocilizumab and corticosteroids should be instituted as indicated in Table 1.
- In the exceptional case where tocilizumab is not available, ensure that suitable alternative measures to treat CRS instead of tocilizumab are available on site.
- Patients who experience CRS should be closely monitored for cardiac and organ functioning until resolution of symptoms.
- For severe or life-threatening CRS, intensive care unit level monitoring and supportive therapy should be considered.
- If concurrent neurologic toxicity is suspected during CRS, administer:
  - Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Table 1 and Table 2;
  - Tocilizumab according to the CRS grade in Table 1;
  - Anti-seizure medication according to the neurologic toxicity grade in Table 2.

Table 1: Cytokine Release Syndrome Grading and Management Guidance

CRS Grade[1]	Tocilizumab	Corticosteroids[a]
Grade 1:		
Fever	If 72 hours or more after infusion, treat symptomatically. If less than 72 hours after infusion, consider tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).	If 72 hours or more after infusion, treat symptomatically. If less than 72 hours after infusion, consider dexamethasone 10 mg IV every 24 hours.
Grade 2:		
Symptoms require and respond to moderate intervention. Fever, oxygen requirement less than 40% FiO_2 or hypotension responsive to fluids, or low dose of one vasopressor, or Grade 2 organ toxicity.	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).	If 72 hours or more after infusion, consider dexamethasone 10 mg IV every 12 to 24 hours. If less than 72 hours after infusion, administer dexamethasone 10 mg IV every 12 to 24 hours.
	If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (10 mg to 20 mg IV every 6 to 12 hours). If no improvement or continued rapid progression, maximise dexamethasone, switch to high-dose methylprednisolone 2 mg/kg if needed. After 2 doses of tocilizumab, consider alternative immunosuppressants. Do not exceed 3 doses tocilizumab in 24 hours, or 4 doses in total.	

Grade 3:		
Symptoms require and respond to aggressive intervention. Fever, oxygen requirement greater than or equal to 40% FiO_2, or hypotension requiring high-dose or multiple vasopressors, or Grade 3 organ toxicity or Grade 4 transaminitis.	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). If no improvement within 24 hours or rapid progression of CRS, escalate tocilizumab and corticosteroid use as per Grade 2.	Administer dexamethasone 10 mg IV every 12 hours.
Grade 4:		
Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous haemodialysis, or Grade 4 organ toxicity (excluding transaminitis).	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). If no improvement within 24 hours or rapid progression of CRS, escalate tocilizumab and corticosteroid use as per Grade 2.	Administer dexamethasone 20 mg IV every 6 hours.

[a] If corticosteroids are initiated, continue for at least 3 doses or until complete resolution of symptoms, and consider corticosteroid taper.

Abbreviations: CRS, cytokine release syndrome; FiO_2, fraction of inspired oxygen; IV, intravenously.

7. NEUROLOGIC TOXICITY INCLUDING ICANS

7.1. Signs and Symptoms of Neurologic Toxicity including ICANS

In clinical studies, the most common manifestations of neurologic toxicity for patients who receive Breyanzi included encephalopathy, tremor, aphasia, delirium, headache, ataxia and dizziness. Seizures and, uncommonly, cerebral oedema have also occurred in patients treated with Breyanzi. Refer to the Israeli Prescribing Information Section 4.4. (Special warnings and precautions for use) and Section 4.8 (Undesirable effects) for a more complete description of the presentation of neurologic toxicity in the Breyanzi clinical trials.

There have been reports of fatal events of ICANS in the post-marketing setting.

7.2. Grading of Neurologic Toxicity Events

Patients should be monitored for neurologic toxicities. The neurologic toxicity grade is determined by the most severe neurotoxicity event not attributable to any other cause. Refer to Table 2 for a description of the neurologic toxicity grade including presenting symptoms.

7.3. Management of Neurologic Toxicity including ICANS

- Patients should be monitored for signs and symptoms of neurologic toxicities 2 to 3 times during the first week following infusion. Frequency of monitoring after the first week should be carried out at the physician's discretion and continued for at least 4 weeks following infusion.
- Counsel patients to seek immediate medical attention should signs and symptoms of neurologic toxicity occur at any time.
- If neurologic toxicity is suspected, it is to be managed according to the recommendations in Table 2. Other causes of neurologic symptoms should be ruled out, including vascular events. Intensive care supportive therapy should be provided for severe or life-threatening neurologic toxicities.
- If concurrent CRS is suspected during neurologic toxicity, administer:
  - Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Table 1 and Table 2;

- Tocilizumab according to the CRS grade in Table 1;
- Anti-seizure medication according to the neurologic toxicity grade in Table 2.

Table 2: Neurologic Toxicity (NT) Including ICANS Grading and Management Guidance

Neurologic Toxicity Grade Including Presenting Symptoms[a]	Corticosteroids and Anti-seizure Medications
Grade 1*	
Mild or asymptomatic. or ICE score 7-9[b] or Depressed level of consciousness[c]: awakens spontaneously.	Start non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. If 72 hours or more after infusion, observe patient. If less than 72 hours after infusion, dexamethasone 10 mg IV every 12 to 24 hours for 2 to 3 days.
Grade 2*	
Moderate. or ICE score 3-6[b] or Depressed level of consciousness[c]: awakens to voice.	Start non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Dexamethasone 10 mg IV every 12 hours for 2 to 3 days, or longer for persistent symptoms. Consider taper for a total corticosteroid exposure of greater than 3 days. If no improvement after 24 hours or worsening of neurologic toxicity, increase the dose and/or frequency of dexamethasone up to a maximum of 20 mg IV every 6 hours.

	If no improvement after another 24 hours, rapidly progressing symptoms, or life-threatening complications arise, give methylprednisolone (2 mg/kg loading dose, followed by 2 mg/kg divided 4 times a day; taper within 7 days).
Grade 3*	
Severe or medically significant but not immediately life threatening; hospitalization or prolongation; disabling. or ICE score 0-2[b] *if ICE score is 0, but the patient is arousable (e.g., awake with global aphasia) and able to perform assessment.* or Depressed level of consciousness[c]: awakens only to tactile stimulus, or Seizures[c], either: • any clinical seizure, focal or generalised, that resolves rapidly, or • non-convulsive seizures on EEG that resolve with intervention,	Start non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Dexamethasone 10 mg to 20 mg IV every 8 to 12 hours. Corticosteroids are not recommended for isolated Grade 3 headaches. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to methylprednisolone (2 mg/kg loading dose, followed by 2 mg/kg divided 4 times a day; taper within 7 days). If cerebral oedema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1 g to 2 g, repeat every 24 hours if needed; taper as clinically indicated) and cyclophosphamide 1.5 g/m^2.

or Raised ICP[c]: focal/local oedema on neuroimaging.	
Grade 4*	
Life threatening. or ICE score 0[b] or Depressed level of consciousness[c], either: • Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • Stupor or coma, or Seizures[c], either: • Life-threatening prolonged seizure (> 5 min), or • Repetitive clinical or electrical seizures without return to baseline in between, or Motor findings[c]: • Deep focal motor weakness such as hemiparesis or paraparesis, or,	Start non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Dexamethasone 20 mg IV every 6 hours. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to methylprednisolone (2 mg/kg loading dose, followed by 2 mg/kg divided 4 times a day; taper within 7 days). If cerebral oedema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1 g to 2 g, repeat every 24 hours if needed; taper as clinically indicated) and cyclophosphamide 1.5 g/m^2.

Raised ICP/cerebral oedema[c], with signs/symptoms such as:

- Diffuse cerebral oedema on neuroimaging, or
- Decerebrate or decorticate posturing, or
- Cranial nerve VI palsy, or
- Papilledema, or
- Cushing's triad.

Abbreviations:
ICE=Immune effector cell-associated encephalopathy;
EEG=Electroencephalogram;
ICP=Intracranial pressure;
IV=intravenously.

* Grading per NCI CTCAE or ASTCT/ICANS

a Management is determined by the most severe event, not attributable to any other cause.

b If patient is arousable and able to perform ICE Assessment, assess: Orientation (oriented to year, month, city, hospital = 4 points); Naming (name 3 objects, e.g., point to clock, pen, button = 3 points); Following Commands (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); Writing (ability to write a standard sentence = 1 point); and Attention (count backwards from 100 by ten = 1 point).
If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.

c Attributable to no other cause.

8. TRANSGENE ASSAY SERVICE TESTING OF SECONDARY MALIGNANCIES

Patients treated with Breyanzi may develop secondary malignancies. Patients should be monitored life-long for secondary malignancies.

If a secondary malignancy is identified to be of T-cell origin, or if it is suspected to be causally related to Breyanzi, the company should be contacted to obtain instructions on the collection of tumour samples for transgene testing. HCPs should inform their patients about the importance of providing consent to transfer their samples to BMS for transgene testing.

A sample of the tumour with confirmed active disease involvement will be requested to test for the presence of Breyanzi transgene. The most appropriate specimen for testing is the original diagnostic tumour sample previously collected and used for the diagnosis of the secondary malignancy. If the original diagnostic tumour sample is not available, a tumour sample collected after diagnosis and confirmed to have involvement with the secondary malignancy is acceptable. In the case of a secondary malignancy with bone marrow involvement, bone marrow aspirate is the preferred specimen over bone marrow biopsy for testing, if available. In addition to tumour samples, peripheral blood collected during the diagnosis of the secondary malignancy may also be requested for testing.

If Breyanzi transgene levels are detected at qualifying levels in the tumour specimen, insertion site analysis will be performed to assess the clonality of the transduced cell population by identifying the frequency and location of insertion sites to ascertain if insertional mutagenesis is suspected in the development of the malignancy. If insertional mutagenesis is suspected, further testing may be conducted to investigate the involvement of the Gene Modified Cell Therapy with the secondary malignancy.

Details for the types and amounts of tumour and blood samples acceptable for testing, and information about the tests that will be performed can be found in the Observational Protocol CA082085 Transgene Assay Service on clinicaltrials.gov website under the study NCT06357754.

Results of testing can be provided to the reporting HCP upon request.

If a secondary malignancy occurs after treatment with Breyanzi, HCPs are asked to contact the company directly via the following: 1809-388054 (a toll-free number) or email: MedInfo.Israel@bms.com

9. PATIENT COUNSELLING

Advise the patient to read the package leaflet.

Talk to the patient about the risks of CRS, neurologic toxicity including ICANS, and secondary malignancy of T-cell origin. Advise them to seek immediate medical care for any of the following:

Neurologic Adverse Reactions	Cytokine Release Syndrome
The following may be symptoms of ICANS: • Confusion • Being less alert (decreased consciousness) • Difficulty speaking or slurred speech • Shaking (tremor) • Feeling anxious • Feeling dizzy • Headache	• Fever • Chills or shaking • Feeling tired • Fast or uneven heartbeat • Feeling light-headed and short of breath • Hypotension

Advise patients to talk to their doctor if they experience new swelling of the glands (lymph nodes) or changes in their skin, such as new rashes or lumps, which may be signs of a new type of cancer.

Provide the patient with the Patient Card, and inform them:

- The symptoms to look for are also provided on the Patient Card.
- They need to carry the Patient Card at all times and always show it to the doctor or nurse when they see them or if they go into hospital.
- The batch number and contact details will be filled in by their Breyanzi-treating physician on the Patient Card.

Advise patients of the need to:

- Remain within proximity of the qualified treatment centre for at least 4 weeks following infusion.
- Refrain from driving or operating heavy or potentially dangerous machines for at least 8 weeks after Breyanzi infusion.

10. 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
- BMS by phone: 1809-388054 (a toll-free number) or email: MedInfo.Israel@bms.com

11. 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: 1809-388054 (a toll-free number) or email: MedInfo.Israel@bms.com

12. REFERENCES

1. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124(2):188-95. Errata in Blood: 2015;126(8):1048 and Blood 2016;128(11):1533.

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