PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**BREYANZI ®**

lisocabtagene maraleucel

Cell suspension in patient-specific single-dose vials, 60 x 10^6 to 120 x 10^6 chimeric antigen receptor (CAR)-positive viable T cells (consisting of CD4 and CD8 components at a ratio range from 0.8 to 1.2), for intravenous infusion

Professed Standard

Other antineoplastic agent (Anatomical Therapeutic Chemical index code: L01X)

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RECENT MAJOR LABEL CHANGES

[Section number and heading], [Subsection number and heading]	[MM/YYYY]

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Breyanzi® (lisocabtagene maraleucel) is a CD19-directed genetically modified autologous T cell immunotherapy indicated for:

- the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

1.1 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Breyanzi in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): In the clinical trial of Breyanzi, 71 (40%) of the 176 patients were 65 years of age or older, and 15 (9%) were 75 years of age or older.

2 CONTRAINDICATIONS

Breyanzi is contraindicated in patients who are hypersensitive to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Cytokine Release Syndrome (CRS)**, including fatal or life-threatening reactions, can occur following treatment with Breyanzi. Delay the infusion of Breyanzi if the patient has unresolved serious events (including pulmonary events, cardiac events, or hypotension), including those after preceding chemotherapies, active uncontrolled infection or inflammatory disorder, or active graft-versus-host disease (GVHD). Monitor for CRS after treatment with Breyanzi. Treat severe or life-threatening CRS with tocilizumab with or without corticosteroids (see 7 WARNINGS AND PRECAUTIONS).
- **Neurologic toxicities**, which may be severe or life-threatening, occurred following treatment with Breyanzi, including concurrently with CRS, after CRS resolution or in the absence of CRS. Monitor for neurologic events after treatment with Breyanzi. Provide supportive care and/or corticosteroids as needed (see 7 WARNINGS AND PRECAUTIONS).
- Breyanzi must be administered under the supervision of healthcare professionals experienced in hematological malignancies at a qualified treatment centre (see 7 WARNINGS AND PRECAUTIONS).

4 DOSAGE AND ADMINISTRATION

For autologous use only. For intravenous use only.

Breyanzi must be administered in a qualified treatment centre under the supervision of healthcare professionals experienced in the treatment of hematological malignancies, and trained for administration and management of patients treated with Breyanzi (see 7 WARNINGS AND PRECAUTIONS).

4.1 Dosing Considerations

- For autologous use only as a single infusion product.
- Do not infuse Breyanzi if the information on the patient-specific label does not match the intended patient.
- For intravenous use only; do not use a leukodepleting filter.
- Do not irradiate Breyanzi.
- Delay the infusion of Breyanzi if the patient has unresolved serious events (including pulmonary events, cardiac events, or hypotension), including those after preceding chemotherapies, active uncontrolled infection or inflammatory disorder, or active graft-versus-host disease (GVHD).
- Ensure that 2 doses of tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment are available per patient prior to infusion of Breyanzi.

4.2 Recommended Dose and Dosage Adjustment

Adults

- Breyanzi is provided as a single-dose, one-time treatment.
- A single dose of BREYANZI contains 60 x 10^6 to 120 × 10^6 CAR-positive viable T cells (consisting of CD4 and CD8 components at a ratio range from 0.8 to 1.2), with each component supplied separately in one to four single-dose vials.
- See the respective Certificate of Release for Infusion (RFI Certificate) for each component, for the actual cell counts and volumes to be infused.

Pediatrics (< 18 years of age)

Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥ 65 years of age)

No dose adjustments are required for patients 65 years of age or older. No clinically important differences in safety or effectiveness of Breyanzi were observed between these patients and younger patients.

4.3 Reconstitution

Not Applicable.

4.4 Administration

Breyanzi is for autologous use only. The patient's identity must match the patient identifiers on the Breyanzi cartons, vials and syringe labels. Do not infuse Breyanzi if the information on the patient-specific label does not match the intended patient.

Ensure that 2 doses of tocilizumab and emergency equipment are available prior to infusion and during the recovery period (see 7 WARNINGS AND PRECAUTIONS).

4.4.1 Preparing the Patient for Breyanzi infusion

Confirm the availability of Breyanzi before starting lymphodepleting chemotherapy.

Pre-treatment conditioning (lymphodepleting chemotherapy)

- Administer the lymphodepleting chemotherapy regimen before infusion of Breyanzi: fludarabine 30 mg/m^2/day intravenously (IV) and cyclophosphamide 300 mg/m^2/day IV for 3 days.
- See the Product Monographs for fludarabine and cyclophosphamide for information on dose adjustment in renal impairment.
- Breyanzi is to be administered 2 to 7 days after completion of lymphodepleting chemotherapy.
- Delay the infusion of Breyanzi if the patient has unresolved serious events (including pulmonary events, cardiac events, or hypotension), including those after preceding chemotherapies, active uncontrolled infection or inflammatory disorder, or active graft-versus-host disease (GVHD).

Pre-medication

- To minimize the risk of infusion reactions, pre-medicate the patient with acetaminophen (650 mg orally) and diphenhydramine (25-50 mg, IV or orally), or another H1-antihistamine, approximately 30 to 60 minutes prior to treatment with Breyanzi.
- Avoid prophylactic use of systemic corticosteroids, as they may interfere with the activity of Breyanzi.

4.4.2 Receipt of Breyanzi

- Breyanzi is shipped directly to the cell associated lab or clinical pharmacy associated with the infusion center in the vapour phase of a liquid nitrogen shipper.
- Confirm the patient's identity with the patient identifiers on the shipper.
- If the patient is not expected to be ready for administration before the shipper expires and the infusion site is qualified for onsite storage, transfer Breyanzi to onsite vapour phase of liquid nitrogen storage prior to preparation.
- If the patient is not expected to be ready for administration before the shipper expires and the infusion site is not qualified for onsite storage, contact Cell Therapy 360 at 1-855-999-0170 to arrange for return shipment.

4.4.3 Preparing Breyanzi

***Before** thawing the vials*

- Confirm the patient's identity with the patient identifiers on the shipper, external Breyanzi carton and the RFI Certificate.
- The Breyanzi vials must not be removed from the carton if the information on the patient-specific label does not match the intended patient. Contact Cell Therapy 360 at 1-855-999-0170 immediately if there are any discrepancies between the labels and the patient identifiers.
- Read the RFI Certificate (affixed inside the shipper) for information on the number of syringes you will need to administer the CD8 and CD4 components (syringe labels are provided with the RFI Certificate). There is a separate RFI Certificate for each cell component.
- 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.

Thawing the vials

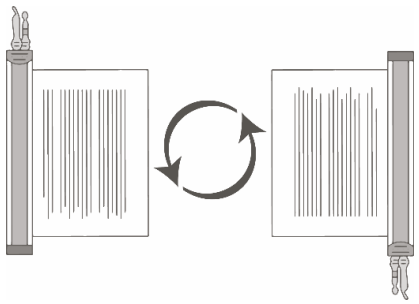
1. Confirm the patient's identity with the patient identifiers on the outer carton and on the syringe labels.
   Once the vials of CAR-positive viable T cells (CD8 component and CD4 component) are removed from frozen storage, the thaw must be carried to completion and the cells administered within 2 hours.
2. Remove the CD8 component carton and CD4 component carton from the outer carton.
3. Confirm the patient's identity with the patient identifiers on the inner carton.
4. Open each inner carton and visually inspect the vial(s) for damage. If the vials are damaged, contact Cell Therapy 360 at 1-855-999-0170.
5. Confirm the patient's identity with the patient identifiers on the vials.
6. Carefully remove the vials from the cartons, place vials on a protective barrier pad, and thaw at room temperature until there is no visible ice in the vials. Thaw all of the vials at the same time. **Keep the CD8 and CD4 components separate**.

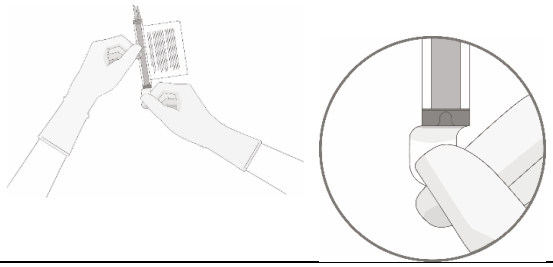
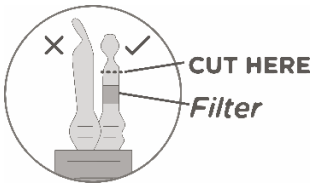
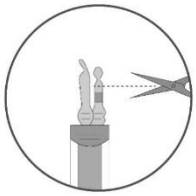
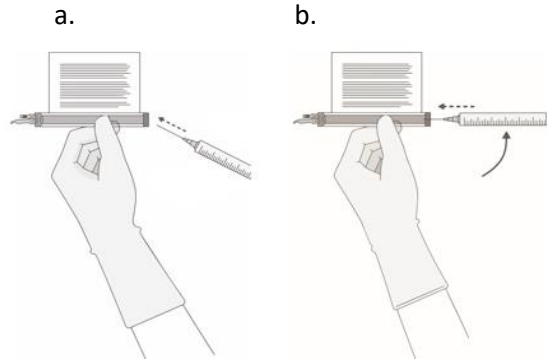
Dose preparation

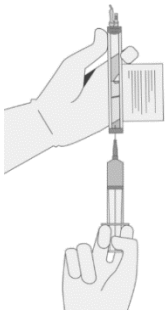
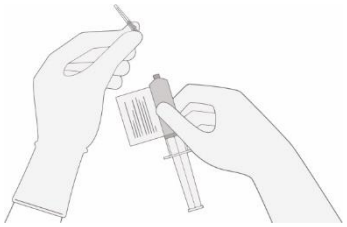
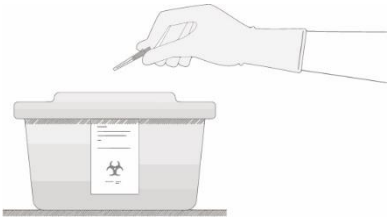
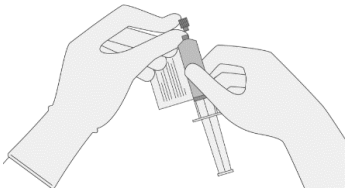
- Prepare Breyanzi using sterile technique.
- Based on the concentration of CAR-positive viable T cells for each component, more than one vial of each of the CD8 and CD4 components may be required to complete a dose. A separate syringe should be prepared for each CD8 or CD4 component vial received.
- **Note:** The volume to be drawn up and infused may differ for each component as indicated on the RFI Certificate. DO NOT draw up excess volume into the syringe.
- Each vial contains 5 mL with a total extractable volume of 4.6 mL of CD8 or CD4 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, 3, or 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.

7. **Prepare the syringe(s) of the CD8 component first.** Confirm that the patient identifiers on the CD8 component syringe label match the patient identifiers on the CD8 component vial label. Affix the CD8 syringe labels to the syringe(s) prior to pulling the required volume into the syringe(s).

Note: It is important to confirm that the volume drawn up for each component matches the volume specified in the respective RFI Certificate. Do NOT draw up excess volume into the syringe.
Withdrawal of the required volume of cells from each vial into a separate syringe should be carried out using the following instructions:

8. Hold the thawed vial(s) upright and gently invert the vial(s) 5 times 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

9. 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 Cell Therapy 360 at 1-855-999-0170. The liquid in the vials should be slightly opaque to opaque, colorless to yellow, or brownish-yellow.	
10. Remove the polyaluminum 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 polyaluminum cover does not impact the sterility of the vial.	
11. 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 <u>with</u> a filter.	 
12. 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.	a. b. 

13. WITHOUT drawing air into the syringe, slowly withdraw the target volume (as specified in the RFI Certificate). Carefully inspect the syringe for signs of debris prior to proceeding. If there is debris, contact Cell Therapy 360 at 1-855-999-0170.	
14. Verify that the volume of CD8/CD4 component matches the volume specified for the relevant component in the RFI Certificate. Once the volume is verified, remove the syringe/needle from the vial, carefully detach the needle from the syringe and cap the syringe.	  
15. Continue to keep the vial horizontal and return it to the carton to avoid leaking from the vial. 16. Dispose of any unused portion of Breyanzi (according to local biosafety guidelines). 17. Repeat the process steps 7-16 for the CD4 component. 18. Transport the labeled CD8 and CD4 syringes to the bedside by placing with protective barrier pad inside an insulated room temperature container.	

4.4.4 Breyanzi Administration

- **Do NOT** use a leukodepleting filter.

- Ensure tocilizumab and emergency equipment are available prior to infusion and during the recovery period (see 7 WARNINGS AND PRECAUTIONS). Consult the Product Monograph for tocilizumab for further information about this drug.
- Confirm the patient's identity matches the patient identifiers on the syringe label.
- Once Breyanzi has been drawn into syringes, proceed with administration as soon as possible. The total time from removal from frozen storage to patient administration should not exceed 2 hours as indicated by the time entered on the syringe label.

1. Use intravenous normal saline to flush all the infusion tubing prior to and after each CD8 or CD4 component administration.
2. Administer the entire volume of the CD8 component intravenously at an infusion rate of approximately 0.5 mL/minute, using the closest port or Y-arm.
   NOTE: The time for infusion will vary but will usually be less than 15 minutes for each component.
3. If more than one syringe is required for a full cell dose of the CD8 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).
4. After the CD8 component has been administered, flush the tubing with normal saline, using enough volume to clear the tubing and the length of the IV catheter.
5. Administer the CD4 component second, immediately after administration of the CD8 component is complete, using the same steps 1-4, as described for the CD8 component. Following administration of the CD4 component, flush the tubing with normal saline, using enough volume to clear the tubing and the length of the IV catheter.

Breyanzi contains human blood cells that are genetically modified with replication incompetent, self-inactivating lentiviral vector. Follow universal precautions and local biosafety guidelines applicable for the handling and disposal, to avoid potential transmission of infectious diseases (see 12 SPECIAL HANDLING INSTRUCTIONS).

4.4.5 Monitoring

- Administer Breyanzi at a qualified treatment centre.
- Monitor patients 2-3 times during the first week following infusion at the qualified treatment centre, for signs and symptoms of CRS and neurologic toxicities.
- Instruct patients to remain within proximity of the qualified treatment centre for at least 4 weeks following infusion.
- Patients should refrain from driving or hazardous activities for 8 weeks.

4.5 Missed Dose

Not applicable.

5 OVERDOSAGE

No data from clinical studies are available regarding overdosage of Breyanzi.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well

as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous Infusion	Breyanzi is a cell suspension for infusion. A single dose contains 60 x 10^6 to 120 × 10^6 CAR-positive viable T cells (consisting of CD4 and CD8 components at a ratio range from 0.8 to 1.2), with each component supplied separately in single-dose vials. CD8 component Vials containing ≥ 8.0 × 10^6 CAR-positive viable T cells in 4.6 mL (≥ 1.6 x 10^6 CAR-positive viable T cells/mL). CD4 component Vials containing ≥ 8.0 × 10^6 CAR-positive viable T cells in 4.6 mL (≥ 1.6 x 10^6 CAR-positive viable T cells/mL). More than one vial of each of the CD8 component and/or CD4 component may be needed to achieve the dose of Breyanzi. The infusion volume is calculated based on the cryopreserved drug product CAR-positive viable T cell concentration. The volume may differ for each component infused. See the Certificate of Release for Infusion (RFI Certificate) for details.	The Breyanzi formulation contains 1% (v/v) of 25% albumin (human), 75% (v/v) Cryostor® CS10 [containing 7.5% dimethylsulfoxide (DMSO) (v/v)], 24% (v/v) Multiple Electrolytes for Injection, Type 1.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.**

General

Breyanzi should be administered at a qualified treatment centre with healthcare professionals trained in handling and administering Breyanzi and in the management of patients treated with Breyanzi, including monitoring and managing cytokine release syndrome (CRS) and neurotoxicity. The centre should have immediate access to appropriate emergency equipment and intensive care unit, and must have on-site, immediate access to tocilizumab. Ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after Breyanzi infusion, if needed for treatment of CRS. Qualified treatment centres must ensure that healthcare professionals who prescribe, dispense, or administer Breyanzi are trained on the management of CRS and neurologic toxicities.

Breyanzi is intended solely for autologous use and under no circumstances be administered to other

patients. Before infusion, the patient's identity must match the patient identifiers on the Breyanzi cartons, vials and syringe labels. Do not infuse Breyanzi if the information on the patient-specific label does not match the intended patient (see 4 DOSAGE AND ADMINISTRATION).

Patients treated with Breyanzi should not donate blood, organs, tissues and cells for transplantation.

There is no experience of use of Breyanzi in patients with primary central nervous system (CNS) lymphoma. For secondary CNS lymphoma, see 14 CLINICAL TRIALS.

Advise the patient to read the Patient Medication Information.

Carcinogenesis and Mutagenesis

Secondary Malignancies

Patients treated with Breyanzi may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Cell Therapy 360 at 1-855-999-0170 for reporting and to obtain instructions on collection of patient samples for testing.

Driving and Operating Machinery

Due to the potential for neurologic events, including altered mental status or seizures with Breyanzi, patients receiving Breyanzi should refrain from driving or operating heavy or potentially dangerous machines for at least 8 weeks after Breyanzi administration.

Endocrine and Metabolism

Tumour lysis syndrome

Tumour lysis syndrome (TLS) has been observed among patients treated with Breyanzi. To minimize the risk of TLS, patients with elevated uric acid or high tumour burden should receive prophylactic treatment (allopurinol, or an alternative prophylaxis) prior to Breyanzi infusion. Signs, symptoms, and laboratory abnormalities of TLS should be monitored and managed according to local practice standards.

Immune

Cytokine release syndrome (CRS)

Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, can occur following treatment with Breyanzi. CRS occurred in 38% (82/213) of patients receiving Breyanzi, including ≥ Grade 3 (Lee grading system[a]) CRS in 3% (7/213) of patients. Among patients who died after receiving Breyanzi, 3 had ongoing CRS events at the time of death. The median time to onset was 4 days (range: 1 to 12 days) and the median duration of CRS was 6 days (range: 1 to 17 days)

Forty-four (21%) patients received tocilizumab and/or a corticosteroid for CRS after infusion of Breyanzi. Twenty-six (12%) patients received tocilizumab only, 16 (8%) received tocilizumab and a corticosteroid, and 2 (1%) received corticosteroids only.

The most common manifestations of CRS include pyrexia (36%), hypotension (20%), tachycardia (15%), chills (11%), and hypoxia (11%). Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, diffuse alveolar damage, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). (see 8 ADVERSE REACTIONS).

Ensure that 2 doses of tocilizumab are available prior to infusion of Breyanzi.

Monitor patients 2-3 times during the first week following infusion at the qualified treatment centre for signs and symptoms of CRS.

Monitor patients for signs or symptoms of CRS for at least 4 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated in Table 2.

Identify cytokine release syndrome (CRS) based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. Breyanzi continues to expand following administration of tocilizumab and corticosteroids. Patients who experience CRS should be closely monitored for cardiac and organ functioning until resolution of symptoms. Patients who experience Grade 2 or higher CRS (e.g., hypotension not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, intensive care unit level monitoring and supportive therapy should be considered.

Patients with high tumour burden or increased inflammatory markers had a higher incidence of CRS, neurologic toxicities, or both of any grade.

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 Tables Table **2** and Table **3**
- Tocilizumab according to the CRS grade in Table 2
- Antiseizure medication according to the neurologic toxicity grade in Table 3.

Table 2: CRS Grading and Management Guidance

CRS Grade[a]	Tocilizumab	Corticosteroids[b]
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). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	If 72 hours or more after infusion, consider dexamethasone 10 mg IV every 12-24 hours. If less than 72 hours after infusion, administer dexamethasone 10 mg IV every 12-24 hours.

Table 2: CRS Grading and Management Guidance

CRS Grade[a]	Tocilizumab	Corticosteroids[b]
	If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (10-20 mg IV every 6 to 12 hours). If no improvement or continued rapid progression, maximize 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% FiO2 or hypotension requiring high-dose or multiple vasopressors, or Grade 3 organ toxicity, or Grade 4 transaminitis.	Per Grade 2	Administer dexamethasone 10 mg/kg IV every 12 hours.
	If no improvement within 24 hours or rapid progression of CRS, repeat tocilizumab and escalate dose and frequency of dexamethasone (10-20 mg IV every 6 to 12 hours). If no improvement or continued rapid progression, maximize 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 4 Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	Administer dexamethasone 20 mg IV every 6 hours.
	If no improvement within 24 hours or rapid progression of CRS, escalate tocilizumab and corticosteroid use. If no improvement or continued rapid progression, maximize 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.	

[a] Lee criteria for grading CRS (Lee DW, Blood 2014; 124(2): 188-95. Errata in Blood: 2015;126(8):1048 and 2016;128(11):1533).
[b] If corticosteroids are initiated, continue corticosteroids for at least 3 doses or until complete resolution of symptoms, and consider corticosteroid taper.

Hypogammaglobulinemia

B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with Breyanzi. Adverse events of hypogammaglobulinemia occurred in 16% (34/213) of patients. Monitor immunoglobulin levels after treatment with Breyanzi and manage using infection precautions, antibiotic prophylaxis, and/or immunoglobulin replacement.

Live Vaccines

The safety of immunization with viral vaccines during or following Breyanzi treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Breyanzi treatment, and until immune recovery following treatment with Breyanzi.

Hypersensitivity

Allergic reactions may occur with the infusion of Breyanzi (see 8 ADVERSE REACTIONS). Serious hypersensitivity reactions, including anaphylaxis, may be due to dimethyl sulfoxide (DMSO).

Prolonged Cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Breyanzi infusion.

Grade 3 or higher cytopenias present at Day 29 following Breyanzi infusion, occurred in 40% (86/213) of patients, and included thrombocytopenia (33%), neutropenia (21%), and anemia (7%). Monitor complete blood counts prior to and after Breyanzi administration.

Infections and Febrile Neutropenia

Breyanzi should not be administered to patients with clinically significant active systemic infections or inflammatory disorders.

Severe infections, including life-threatening or fatal infections, have occurred in patients after Breyanzi infusion. Infections (all grades) occurred in 40% (85/213) of patients. Grade 3 or higher infections occurred in 11% (24/213) of patients. Grade 3 or higher infections with an unspecified pathogen occurred in 8% (18/213) of patients, bacterial infections occurred in 3% (7/213), fungal infections occurred in 2% (4/213), and viral infections occurred in 0.5% (1/213). Monitor patients for signs and symptoms of infection before and after Breyanzi administration and treat appropriately. Administer prophylactic antimicrobials according to standard institutional guidelines.

Febrile neutropenia has been observed in 8% (16/213) of patients after Breyanzi infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad-spectrum antibiotics, fluids, and other supportive care as medically indicated.

Viral Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs directed against B cells.

In clinical trials, there were no reports of hepatitis reactivation in patients with prior history of HBV or worsening of HCV infection in patients treated with Breyanzi. Nine of the 10 patients in the TRANSCEND study with a prior history of HBV were treated with concurrent antiviral suppressive therapy to prevent HBV reactivation during and after Breyanzi therapy.

Screening for HBV, HCV, and HIV should be performed in accordance with clinical guidelines before collection of cells for manufacturing.

Neurologic

Neurologic toxicities

Neurologic toxicities which may be severe or life-threatening, occurred following treatment with Breyanzi, including concurrently with CRS, after CRS resolution, or in the absence of CRS. CAR T cell-associated neurologic toxicities, as identified by investigators, occurred in 28% (59/213) of patients receiving Breyanzi, including Grade 3 or 4 in 9% (20/213) of patients (no Grade 5 events). The median time to onset of the first event was 9 days (range: 1 to 46 days); all of the neurologic toxicities occurred within the first 8 weeks following Breyanzi infusion. The median duration of neurologic toxicities was 9 days range: 1 to 84 days).

The most common neurologic toxicities included encephalopathy (18%), tremor (10%), aphasia (9%), delirium (7%), dizziness (4%), and headache (4%). Seizures and cerebral edema have also occurred in patients treated with Breyanzi.

Monitor patients 2-3 times during the first week following infusion at the qualified treatment centre, for signs and symptoms of neurologic toxicities. Monitor patients for signs or symptoms of neurologic toxicities for at least 4 weeks after infusion and treat promptly. Counsel patients to seek immediate medical attention should signs or symptoms of neurologic toxicity occur at any time.

Monitor patients for signs and symptoms of neurologic toxicities (Table 3). Rule out other causes of neurologic symptoms. Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities. If neurologic toxicity is suspected, manage according to the recommendations in Table 3.

If concurrent CRS is suspected during the neurologic toxicity, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables Table **2** and Table **3**
- Tocilizumab according to the CRS grade in Table 2
- Antiseizure medication according to the neurologic toxicity grade in Table 3.

Table 3: Neurologic Toxicity (NT) Grading and Management Guidance

NT Grade[a]	Corticosteroids and Antiseizure Medication
Grade 1 Examples include: Somnolence-mild drowsiness or sleepiness Confusion-mild disorientation Encephalopathy-mild limiting of activities of daily living (ADLs) Dysphasia-not impairing ability to communicate	Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. If 72 hours or more after infusion, observe. If less than 72 hours after infusion, consider dexamethasone 10 mg IV every 12 to 24 hours for 2 to 3 days.
Grade 2 Examples include: Somnolence—moderate, limiting instrumental ADLs Confusion—moderate disorientation Encephalopathy—limiting instrumental ADLs Dysphasia—moderate impairing ability to communicate spontaneously Seizure(s)	Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Dexamethasone 10 mg IV every 12 hours for 2-3 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).

Table 3: Neurologic Toxicity (NT) Grading and Management Guidance	
NT Grade[a]	**Corticosteroids and Antiseizure Medication**
Grade 3 Examples include: Somnolence—obtundation or stupor Confusion—severe disorientation Encephalopathy—limiting self-care ADLs Dysphasia—severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly	Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Dexamethasone 10 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 (dose and frequency as per Grade 2). If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated) and cyclophosphamide 1.5 mg/m^2.
Grade 4 Life-threatening consequences Urgent intervention indicated Requirement for mechanical ventilation	Start non-sedating, antiseizure 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 (dose and frequency as per Grade 2). If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated), and cyclophosphamide 1.5 mg/m^2.

[a] NCI CTCAE (Common Terminology Criteria for Adverse Events) criteria for grading neurologic toxicities.

Reproductive Health: Female and Male Potential

- ***Reproduction***

Pregnancy status for women of child-bearing age should be verified using a pregnancy test prior to starting treatment with Breyanzi.

Contraception for the partner who will receive Breyanzi, should be discussed as follows:

> Sexually active females of reproductive potential should use effective contraception (methods that result in less than 1% pregnancy rates) after Breyanzi administration.
>
> Sexually active males who have received Breyanzi should use a condom during intercourse with females of reproductive potential or pregnant women.

See the Product Monographs for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with Breyanzi.

- **Fertility**

There are no data on the effect of Breyanzi on fertility.

- **Teratogenic Risk**

There are no data on the teratogenic risk of Breyanzi.

7.1 Special Populations

7.1.1 Pregnant Women

There are no data from the use of Breyanzi in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with Breyanzi to assess whether it can cause fetal harm when administered to a pregnant woman.

It is not known if Breyanzi has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, Breyanzi is not recommended for women who are pregnant, and pregnancy after Breyanzi infusion should be discussed with the treating physician.

Clinical Considerations

Fetal/Neonatal Adverse Reactions
Assessment of immunoglobulin levels and B cells in newborns of mothers treated with Breyanzi should be considered.

7.1.2 Breast-feeding

It is unknown whether Breyanzi cells are excreted in human milk or transferred to the breast-feeding child. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Breyanzi and any potential adverse effects on the breastfed infant from Breyanzi or from the underlying maternal condition. Women who are breast-feeding should be advised of the potential risk to the breast-fed child.

7.1.3 Pediatrics (< 18 years of age)

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Breyanzi in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics (≥ 65 years of age)

In the clinical trial of Breyanzi, 71 (40%) of the 176 patients were 65 years of age or older, and 15 (9%) were 75 years of age or older. No clinically important differences in safety or effectiveness of BREYANZI were observed between these patients and younger patients. No dose adjustments are required for patients 65 years of age or older.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following adverse reactions are described under **WARNINGS AND PRECAUTIONS**:
- Cytokine Release Syndrome
- Hypogammaglobulinemia
- Hypersensitivity
- Prolonged Cytopenias
- Severe Infections
- Neurologic Toxicities

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety data described in this section reflect exposure to BREYANZI based on the pooled data from two studies (TRANSCEND [017001] and TRANSCEND WORLD [JCAR017-BCM-001]) in 213 adult patients within the dose range of 60 x 10^6 to 120 x 10^6 CAR+ viable T cells with R/R large B-cell lymphoma who received a flat dose of BREYANZI (14 CLINICAL TRIALS). The median duration of follow-up was 10.4 months. The median age of the study population was 62 years (range: 18 to 79 years); 66% were men. The Eastern Cooperative Oncology Group (ECOG) performance status at screening was 0 in 40% of patients, 1 in 58% of patients, and 2 in 2% of patients; 62% of patients received anticancer therapy for disease control.

The most common non-laboratory adverse reactions of any grade (≥ 20%) were fatigue (41%), CRS (38%), headache (29%), nausea (29%), diarrhea (25%), encephalopathy (25%), hypotension (23%), cough (23%), infections-pathogen unspecified (23%), pyrexia (23%), abdominal pain (20%), constipation (20%) and dizziness (20%).

Serious adverse reactions were reported in 44% of patients. The most common non-laboratory, serious adverse reactions (>2%) were CRS (16%), aphasia (5%), confusional state (4%), pneumonia (4%), pyrexia (4%), encephalopathy (3%), and hypotension (3%). Eighteen (8%) patients required intensive care unit admission.

The most common non-laboratory Grade 3 or higher adverse reactions (>2%) were infections-pathogen unspecified (8%), febrile neutropenia (8%), encephalopathy (7%), hypotension (5%), abdominal pain (3%), aphasia (3%), CRS (3%), decreased appetite (3%), delirium (3%), dizziness (3%), dyspnea (3%), gastrointestinal haemorrhage (3%), bacterial infection (3%), and renal insufficiency (3%). Grade 5 (fatal) adverse events were reported in 7 patients (cardiomyopathy, leukoencephalopathy (attributed to prior fludarabine exposure), septic shock (considered unrelated to Breyanzi), candida sepsis, pulmonary hemorrhage, multiple organ dysfunction syndrome, and respiratory failure).

Table 4 summarizes the non-laboratory adverse reactions that occurred in at least 10% of patients treated with Breyanzi. Adverse drug reactions (Table 4) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency (%), with the most frequent reactions first.

Table 4: Adverse Reactions Observed in at Least 10% of the Patients Treated with Breyanzi in the TRANSCEND and TRANSCEND WORLD Studies (n = 213)

Adverse Reaction	All Grades n = 213 n (%)	Grade 3 or Higher n = 213 n (%)
Cardiovascular Disorders		
Tachycardia[a]	41 (19)	0 (0)
Gastrointestinal Disorders		
Nausea	62 (29)	5 (2)
Diarrhea	53 (25)	2 (1)
Constipation	43 (20)	0 (0)
Abdominal pain[b]	42 (20)	6 (3)
Vomiting	33 (15)	1 (0.5)
General Disorders and Administration Site Conditions		
Fatigue[c]	88 (41)	4 (2)
Pyrexia	48 (23)	0 (0)
Edema[d]	38 (18)	3 (1)
Immune System Disorders		
Cytokine release syndrome	82 (38)	7 (3)
Hypogammaglobulinemia[e]	34 (16)	0 (0)
Infections and Infestations[f]		
Infections-pathogen unspecified	48 (23)	18 (8)
Bacterial infectious disorders	23 (11)	7 (3)
Nervous System Disorders		
Headache[g]	61 (29)	3 (1)
Encephalopathy[h]	53 (25)	14 (7)
Dizziness[i]	43 (20)	6 (3)
Tremor[j]	33 (15)	1 (0.5)
Psychiatric Disorders		
Insomnia[k]	25 (12)	1 (0.5)
Renal and Urinary Disorders		
Renal insufficiency[l]	23 (11)	6 (3)

Table 4: Adverse Reactions Observed in at Least 10% of the Patients Treated with Breyanzi in the TRANSCEND and TRANSCEND WORLD Studies (n = 213)

Adverse Reaction	All Grades n = 213 n (%)	Grade 3 or Higher n = 213 n (%)
Respiratory, Thoracic and Mediastinal Disorders		
Cough[m]	49 (23)	0 (0)
Dyspnea[n]	34 (16)	7 (3)
Vascular Disorders		
Hypotension[o]	50 (23)	11 (5)

[a] Tachycardia includes heart rate increased, sinus tachycardia, tachycardia.
[b] Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal rigidity, abdominal tenderness.
[c] Fatigue includes fatigue, malaise.
[d] Edema includes edema, edema genital, edema peripheral, generalized edema, localized edema, scrotal edema, peripheral swelling, swelling.
[e] Hypogammaglobulinemia includes Hypogammaglobulinaemia, Immunoglobulins decreased
[f] Infections and infestations are grouped per MedDRA high level group term.
[g] Headache includes headache, head discomfort, migraine, sinus headache.
[h] Encephalopathy includes amnesia, cognitive disorder, confusional state, depersonalization/derealization disorder, depressed level of consciousness, disturbance in attention, encephalopathy, flat affect, hypersomnia, incoherent, lethargy, leukoencephalopathy, loss of consciousness, memory impairment, mental impairment, mental status changes, somnolence.
[i] Dizziness includes dizziness, presyncope, syncope.
[j] Tremor includes tremor, essential tremor, resting tremor
[k] Insomnia includes insomnia, somnambulism.
[l] Renal insufficiency includes acute kidney injury, blood creatinine increased, renal failure, renal injury.
[m] Cough includes cough, productive cough, upper-airway cough syndrome.
[n] Dyspnea includes acute respiratory failure, dyspnea, dyspnea exertional, respiratory failure.
[o] Hypotension includes hypotension, orthostatic hypotension.

8.3 Less Common Clinical Trial Adverse Reactions

Other clinically important adverse reactions that occurred in less than 10% of patients treated with Breyanzi include the following:

- *Blood and lymphatic system disorders:* Febrile neutropenia (7.5%), histiocytosis hematophagic (0.9%)
- *Cardiac disorders:* Arrhythmia[a] (6.6%), cardiomyopathy (1.4%)
- *Gastrointestinal disorders:* Gastrointestinal hemorrhage[b] (4.2%)
- *General disorders and administration site conditions:* Chills (7.5%)
- *Infections and infestations[c]:* Viral infectious disorders (9.9%) Fungal infectious disorders (6.6%)
- *Injury, poisoning, and procedural complications:* Infusion-related reaction (1.9%)
- *Metabolism and nutrition disorders:* Tumour lysis syndrome (0.5%)
- *Nervous system disorders:* Aphasia (9.9%), peripheral neuropathy (9.9%) visual disturbance[e] (5.6%), ataxia/gait disturbance[d] (3.8%), cerebellar syndrome[f] (3.8%), cerebrovascular events[g] (1.9%), seizure[h] (0.9%), facial paralysis (0.9%), brain edema (0.5%)
- *Psychiatric disorders:* Delirium[i] (9.9%), Anxiety (8.5%)

• *Respiratory, thoracic and mediastinal disorders:* Pleural effusion (6.1%), hypoxia (4.2%), pulmonary edema (0.9%)
• *Vascular disorders:* Hypertension[j] (9.9%), thrombosis[k] (4.7%)

[a] Arrhythmia includes arrhythmia, atrial fibrillation, atrioventricular block complete, atrioventricular block second degree, supraventricular tachycardia, ventricular tachycardia.
[b] Gastrointestinal hemorrhage includes gastrointestinal hemorrhage, gastric ulcer hemorrhage, hematochezia, melena, rectal hemorrhage, upper gastrointestinal hemorrhage.
[c] Infections and infestations are grouped by MedDRA high level group term.
[d] Ataxia/gait disturbance includes ataxia, gait disturbance.
[e] Visual disturbance includes blindness, blindness unilateral, gaze palsy, mydriasis, nystagmus, vision blurred, visual field defect.
[f] Cerebellar syndrome includes balance disorder, cerebellar syndrome, dyskinesia, dysmetria, hand-eye coordination impaired.
[g] Cerebrovascular events include cerebral infarction, cerebral venous thrombosis, cerebrovascular accident, hemorrhage intracranial, transient ischemic attack.
[h] Seizure includes seizure, status epilepticus.
[i] Delirium includes agitation, delirium, delusion, disorientation, hallucination, 'hallucination, visual', irritability, restlessness
[j] Hypertension includes hypertension, orthostatic hypertension.
[k] Thrombosis includes deep vein thrombosis, embolism, pulmonary embolism, thrombosis, venous thrombosis limb, vena cava thrombosis.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Table 5 describes the treatment-emergent laboratory abnormalities of Grade 3 or 4 that occurred in at least 10% of patients.

Table 5: Grade 3 or 4 Treatment-emergent Laboratory Abnormalities Occurring in ≥ 10% of Patients Following Treatment with Breyanzi in the TRANSCEND and TRANSCEND WORLD Studies, Based on NCI CTCAE[a] (n = 213)

Laboratory Abnormality	Grade 3 or 4 n (%) n = 213
Neutropenia	157 (74)
Leukopenia	110 (52)
Thrombocytopenia	82 (38)
Anemia	48 (23)
Hypophosphatemia	29 (14)

[a] NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03

Immunogenicity

Breyanzi has the potential to induce anti-product antibodies. The immunogenicity of Breyanzi has been evaluated using an electrochemiluminescence (ECL) immunoassay for the detection of binding antibodies against the extracellular CD19-binding domain of Breyanzi. Pre-existing anti-product antibodies were detected in 9% (18/209) of patients. Treatment-induced or treatment-boosted anti-

product antibodies were detected in 16% (32/202) of patients. Due to the small number of patients who had anti-product antibodies, the relationship between anti-product antibody status and efficacy, safety, or pharmacokinetics was not conclusive.

8.5 Post-Market Adverse Reactions

Currently there are no post-marketing adverse reactions data available.

9 DRUG INTERACTIONS

9.1 Drug Interactions Overview

No interaction studies have been performed in humans.

9.2 Drug-Drug Interactions

Interactions with other drugs have not been established.

Pharmacokinetic Interactions

No pharmacokinetic drug interaction studies have been performed with Breyanzi. T-cells are known to be susceptible to immune-suppressive agents. The benefit/risk of immuno-suppressive agents including but not limited to corticosteroids, cytotoxic chemotherapy, immunophilins, mTOR inhibitors, should be considered as these can be lymphotoxic and may reduce the effectiveness of Breyanzi (see 10 CLINICAL PHARMACOLOGY - 10.3 Pharmacokinetics).

Pharmacodynamic Interactions

Monoclonal antibodies directed against the epidermal growth factor receptor (anti-EGFR mAbs)

Anti-EGFR mAbs (e.g., cetuximab, panitumumab) could potentially reduce the number of Breyanzi cells as a truncated EGFR is expressed on the CAR T cells and thereby may reduce Breyanzi benefit. Prescribers should carefully assess benefit and risk before using anti-EGFR mAb therapy.

Live vaccines

The safety of immunization with live viral vaccines during or following Breyanzi treatment has not been studied. The effectiveness of vaccines may be affected by prolonged B-cell aplasia and hypogammaglobulinemia (see 7 WARNINGS AND PRECAUTIONS). Vaccination with live viral vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Breyanzi treatment, and until immune recovery following treatment with Breyanzi.

9.3 Drug-Food Interactions

Interactions with food have not been established.

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.5 Drug-Laboratory Test Interactions

HIV and the lentivirus used to make Breyanzi have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid tests may yield false-positive results in patients who have received Breyanzi.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Breyanzi is a CD19-directed genetically modified autologous cellular immunotherapy administered as a defined composition to reduce variability in CD8-positive and CD4-positive T cell dose. The CAR is comprised of an FMC63 monoclonal antibody-derived single chain variable fragment (scFv), IgG4 hinge region, CD28 transmembrane domain, 4-1BB (CD137) costimulatory domain, and CD3 zeta activation domain. CD3 zeta signaling is critical for initiating T-cell activation and antitumour activity, while 4-1BB (CD137) signaling enhances the expansion and persistence of Breyanzi. In addition, Breyanzi includes a nonfunctional truncated epidermal growth factor receptor (EGFRt) that is co-expressed on the cell surface with the CD19-specific CAR.

CAR binding to CD19 expressed on the cell surface of tumour and normal B cells induces activation and proliferation of CAR T cells, release of pro-inflammatory cytokines, and cytotoxic killing of target cells.

10.2 Pharmacodynamics

Following Breyanzi infusion, pharmacodynamic responses were evaluated over a 4-week period by measuring transient elevation of soluble biomarkers such as cytokines, chemokines, and other molecules. Peak elevation of soluble biomarkers was observed within the first 14 days after Breyanzi infusion and returned to baseline levels within 28 days.

B-cell aplasia, defined as CD19-positive B cells comprising less than 3% of peripheral blood lymphocytes, is an on-target effect of Breyanzi. B-cell aplasia was observed in the majority of patients for up to 1 year following Breyanzi infusion.

10.3 Pharmacokinetics

Following infusion, Breyanzi exhibited an initial expansion followed by a bi-exponential decline. The median time of maximal expansion in peripheral blood occurred 11 days after the first infusion. Breyanzi was present in peripheral blood for up to 2 years.

Responders (N=122) had a 2.17-fold higher median C_{max} than non-responders (N=35) (32,093.2 vs. 14,776.0 copies/µg). Responders had a 1.92-fold higher median $AUC_{0\text{-}28d}$ than non-responders (265,237.5 vs. 138,183.9 day*copies/µg) (see Table 6).

Some patients required tocilizumab and corticosteroids for the management of CRS and neurologic toxicities. Patients treated with tocilizumab (N=33) had a 3.87-fold and 3.69-fold higher median C_{max} and $AUC_{0\text{-}28d}$, respectively, compared to patients who did not receive tocilizumab (N=132). Similarly, patients who received corticosteroids (N=29) had a 4.32-fold and 3.73-fold higher median C_{max} and $AUC_{0\text{-}28d}$, respectively, compared to patients who did not receive corticosteroids (N=136).

- Patients < 65 years old (N=98) had a 2.48-fold and 2.64-fold higher median C_{max} and AUC_{0-28d}, respectively, compared to patients ≥ 65 years old (N=67). Sex, race, ethnicity, and body weight did not show clear relationships to C_{max} and AUC_{0-28d}.

Table 6: Cellular Kinetic Parameters of Breyanzi in Adult Patients with Relapsed or Refractory Large B-cell Lymphoma

Parameter	Responding Patients n = 122	Non-Responding Patients n = 35
C_{max} (copies/µg)		
Median	32,093.2	14,776.0
IQR	13,472.9 - 101,400.8	5,421.0 - 51,968.9
Range	256.9 - 528,736.9	422.5 - 415,118.5
T_{max} (day)		
Median	11.0	14.0
IQR	10.0 - 14.0	10.0 - 15.0
Range	6 - 30	6 - 41
AUC_{0-28d} (day*copies/µg)		
Median	265,237.5	138,183.9
IQR	111,935.2 - 736,225.6	36,538.7 - 507,566.8
Range	2,602 - 5,144, 642	5,522 - 6,646,582

n is the number of patients with evaluable PK parameter. IQR: interquartile range: Q1 – Q3
Response data are based on the Lugano 2014 criteria, as assessed by IRC.

Formal renal impairment and hepatic impairment studies have not been conducted.

11 STORAGE, STABILITY AND DISPOSAL

Storage

Breyanzi consists of genetically modified autologous T cells, supplied in vials as separate frozen suspensions of each CD8 and CD4 component. Each CD8 or CD4 component is packed in a carton containing up to 4 vials, depending upon the cryopreserved drug product CAR-positive viable T cell concentration. The cartons for each CD8 component and CD4 component are contained in an outer carton and shipped in a liquid nitrogen shipper. An RFI Certificate for each component and patient-specific syringe labels are affixed inside the shipper.

- Confirm patient identity upon receipt.
- Store vials in the vapor phase of liquid nitrogen (less than or equal to minus 130°C) in a temperature-monitored system.
- Thaw Breyanzi prior to infusion (see 4 DOSAGE AND ADMINISTRATION).

Stability

- Shelf-life of 13 months for unopened vial when stored in the vapor phase of liquid nitrogen (less than or equal to minus 130°C).
- Once Breyanzi has been drawn into syringes, proceed with administration as soon as possible. The total time from removal from frozen storage to patient administration should not exceed 2 hours at room temperature (15°C -25°C).

Disposal

Breyanzi contains genetically modified human blood cells. Local biosafety guidelines should be followed for unused medicinal products or waste material. 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 biosafety guidelines. Work surfaces which have or may have been in contact with Breyanzi must be decontaminated with appropriate disinfectant.

12 SPECIAL HANDLING INSTRUCTIONS

Breyanzi contains human blood cells that are genetically modified with replication incompetent, self-inactivating lentiviral vector. Follow universal precautions and local biosafety guidelines applicable for handling and disposal to avoid potential transmission of infectious diseases.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

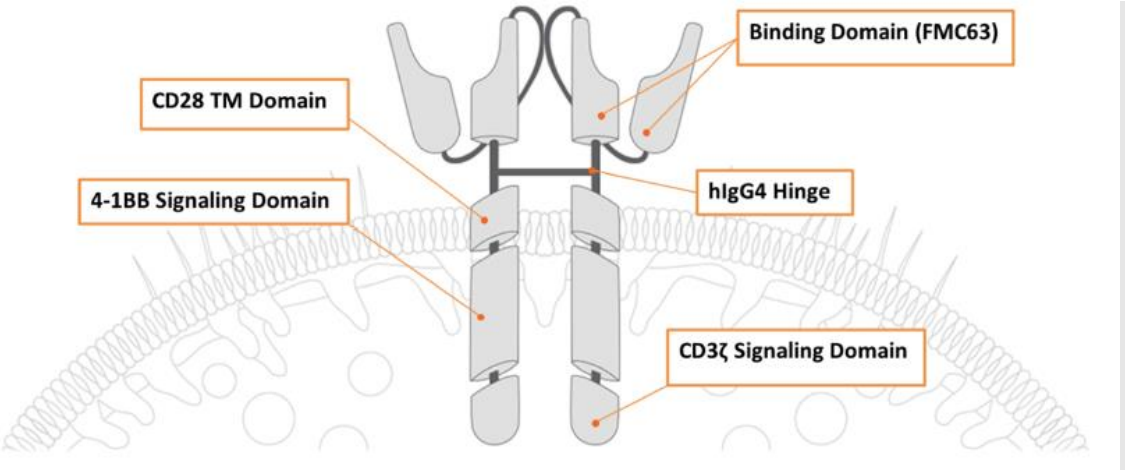
Drug Substance

Proper name: lisocabtagene maraleucel

Chemical name: Not applicable.

Molecular formula and molecular mass: Not applicable.

Structural formula:



Physicochemical properties: lisocabtagene maraleucel is a slightly opaque to opaque, colourless to yellow, or brownish-yellow suspension of cells for infusion.

Pharmaceutical standard: Not applicable, as the drug substance is produced from an individual patient's autologous cells.

Product Characteristics:

Breyanzi is a T-cell product. Breyanzi is prepared from the patient's T cells, which are purified from the product of a standard leukapheresis procedure. The purified CD8-positive and CD4-positive T cells are separately activated and transduced with the replication incompetent lentiviral vector containing the anti-CD19 CAR transgene. The transduced T cells are expanded in cell culture, washed, formulated into a suspension, and cryopreserved as separate CD8 and CD4 component vials that together constitute a single dose of Breyanzi. The product must pass a sterility test before release for shipping as a frozen suspension in patient-specific vials. The product is thawed prior to administration (see 4 DOSAGE AND ADMINISTRATION, 11 STORAGE, STABILITY AND DISPOSAL, 12 SPECIAL HANDLING INSTRUCTIONS).

The Breyanzi formulation contains 1% (v/v) of 25% albumin (human), 75% (v/v) Cryostor® CS10 [containing 7.5% dimethylsulfoxide (DMSO) (v/v)], 24% (v/v) Multiple Electrolytes for Injection, Type 1.

14 CLINICAL TRIALS

Relapsed or Refractory Large B-Cell Lymphoma

14.1 Trial Design and Study Demographics

Table 7: Summary of patient demographics for the clinical trial in relapsed or refractory large B-cell lymphoma

Study	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
TRANSCEND (017001)	Open-label, multicentre, single-arm trial in adult patients with relapsed or refractory large B-cell lymphoma	Single intravenous infusion of Breyanzi within the dose range of 60-120 x 10^6 CAR+ viable T cells (consisting of CD8 and CD4 components)	227 patients underwent leukapheresis; 176 received Breyanzi	Breyanzi - treated group: 59.8 years (range: 18-79)	Breyanzi - treated: 117 (66.5%) males 59 (33.5%) females

The anti-tumour activity and safety of Breyanzi were evaluated in an open-label, multicentre, single-arm trial, TRANSCEND (017001), in patients with relapsed or refractory (R/R) aggressive B-cell non-Hodgkin lymphoma (NHL). Eligible patients were ≥ 18 years with R/R diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS) (n=94); DLBCL transformed from follicular lymphoma (n=33), marginal zone lymphoma (n=4), chronic lymphocytic leukaemia/small lymphocytic leukaemia (n=2), Waldenström's macroglobulinaemia (n=1); high-grade B-cell lymphoma (n=26); primary mediastinal large B-cell lymphoma (PMBCL) (n=14); and follicular lymphoma grade 3B (FL3B) (n=2), who had received at least 2 lines of therapy. The study included patients with ECOG performance status ≤ 2 (three patients with an ECOG PS of 2), prior autologous and/or allogeneic haematopoietic stem cell transplant (HSCT), and secondary central nervous system (CNS) lymphoma involvement. The study excluded patients with a creatinine clearance of less than 30 mL/min, alanine aminotransferase > 5 times the upper limit of normal or, left ventricular ejection fraction < 40%. There was no minimum requirement for blood counts; patients were eligible to enroll if they were assessed by the investigator to have adequate bone marrow function to receive lymphodepleting chemotherapy.

Trial patients had to be clinically stable and must have recovered from prior toxicities to receive lymphodepleting chemotherapy (LDC) and then proceed to Breyanzi infusion. Neither LDC nor Breyanzi was to be administered if there was rapid clinical deterioration, or evidence of rapid progression of disease.

Treatment consisted of lymphodepleting chemotherapy, fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day for 3 days, followed by Breyanzi 2 to 7 days later. The median dose of Breyanzi was 91.3 × 10^6 CAR-positive viable T cells (range: 63-120 × 10^6 CAR-positive viable T cells).

Anticancer therapy for disease control was permitted between apheresis and lymphodepletion. Of the 176 patients treated with Breyanzi, 57% received anticancer therapy, for disease control at the discretion of the investigator.

Of 227 patients who underwent leukapheresis for whom BREYANZI was manufactured in the dose range of 60 x 10^6 to 120 × 10^6 CAR-positive viable T cells:

- 176 received BREYANZI in the intended dose range
- 17 either received BREYANZI outside of the intended dose range (n=1) or received CAR-positive T cells that did not meet the product specifications for BREYANZI (n=16)
- 34 did not receive CAR-positive T cells either due to manufacturing failures (n=1), death (n=24), disease complications (n=4), or other reasons (n=5)

Breyanzi was administered in the inpatient (163 patients) or outpatient (13 patients) setting. Safety and efficacy were consistent across the two groups.

The number of patients who were evaluable for efficacy was 168 (Efficacy set). Eight (8) patients were not evaluable for efficacy because they did not have baseline PET-positive disease, or confirmation of PET positive disease after anticancer therapy for disease control by Independent Review Committee (IRC).

The median time from leukapheresis to product availability was 24.5 days (range: 17 to 51 days), and the median time from leukapheresis to infusion was 36 days (range: 27 to 126 days).

Table 8 summarizes the baseline patient and disease characteristics in the TRANSCEND trial.

Table 8: Baseline Demographic and Disease-related Characteristics

Characteristic	**Breyanzi-treated N= 176**
Median Age, years (range)	63.0 (18,79)
≥ 65 years, n (%)	71 (40.3)
≥ 75 years, n (%)	15 (8.5)
Sex, n (%) Male Female	 117 (66.5) 59 (33.5)
Prior HSCT, n (%) Autologous HSCT Allogeneic HSCT	 61 (34.7) 4 (2.3)
ECOG Performance Status ECOG 0-1, n (%) ECOG 2, n (%)	 173 (98.3) 3 (1.7)
Large B-cell lymphoma subtype, n (%)	
DLBCL, NOS	94 (53.4)
DLBCL transformed from indolent lymphoma	40 (22.7)

Table 8: Baseline Demographic and Disease-related Characteristics

Characteristic	Breyanzi-treated N= 176
Transformed from follicular lymphoma	*33 (18.8)*
Transformed from marginal zone lymphoma	*4 (2.3)*
Transformed from CLL/SLL (Richter syndrome)	*2 (1.1)*
Transformed from Waldenström's macroglobulinaemia	*1 (0.6)*
High-grade B cell lymphoma	26 (14.8)
PMBCL	14 (8.0)
Follicular lymphoma, grade 3B	2 (1.1)
Median number of prior therapies (range)	3 (1 - 8)
Chemorefractory[a] , n (%)	123 (69.9)
Refractory[b], n (%)	142 (80.7)
Relapsed[c], n (%)	34 (19.3)
Secondary CNS lymphoma at time of Breyanzi infusion, n (%)	4 (2.3)
Never achieved CR from prior therapies, n (%)	76 (43.2)

[a] Chemorefractory is defined as experiencing stable disease (SD) or progressive disease (PD) to last chemo-containing regimen or relapsed < 12 months after autologous stem cell transplantation.
[b] The status was refractory if a patient achieved less than a complete response (CR) to last prior therapy.
[c] The status was relapsed if a patient achieved CR to last prior therapy.

14.2 Study Results

Efficacy was established on the basis of the primary endpoint, overall response rate (ORR), in addition to secondary endpoints which included complete response (CR) rate and duration of response (DOR) as determined by an independent review committee (Table 9 and Figure 1).

The median time to response (CR or partial response [PR]) was 0.95 months (range: 0.7 to 8.9 months). The median time to CR was 0.95 months (range 0.8 to 12.5 months). Response durations were longer in patients who achieved a CR, as compared to patients with a best response of PR (Table 9).

Four patients with secondary CNS lymphoma were treated and evaluable for efficacy in the TRANSCEND study. Two of these patients achieved CR; one of two patients had a durable remission of 16.8 months that remained ongoing at the time of data cut-off.

Table 9: Results of the TRANSCEND Study in Relapsed or Refractory Large B-cell Lymphoma	
	Efficacy set n = 168
Primary Endpoint	
Overall response rate[a], n [95% CI]	124 (73.8%) [66.5%, 80.3%]
Secondary Endpoints	
Complete response, n [95% CI]	88 (52.4%) [44.5%, 60.1%]
Partial response, n [95% CI]	36 (21.4%) [15.5%, 28.4%]
Duration of response (DOR)[a,b] **(months)** Median [95% CI][c] Range	n=124 16.8 [6.0-NR] 0.0+, 23.5+
DOR if best response is CR[a,b] **(months)** Median [95% CI][c] Range	n=88 NR [16.8-NR] 1.1, 23.5+
Median follow-up for DOR (months) Median [95% CI][d]	 14.5 [11.4-16.8]

CI=confidence interval; CR=complete response; IRC=Independent Review Committee; KM=Kaplan-Meier; NR=not reached

[a] Per the Lugano 2014 criteria, as assessed by IRC

[b] Deaths after initiation of anti-cancer treatment were considered as events

[c] KM method was used to obtain 2-sided 95% CIs.

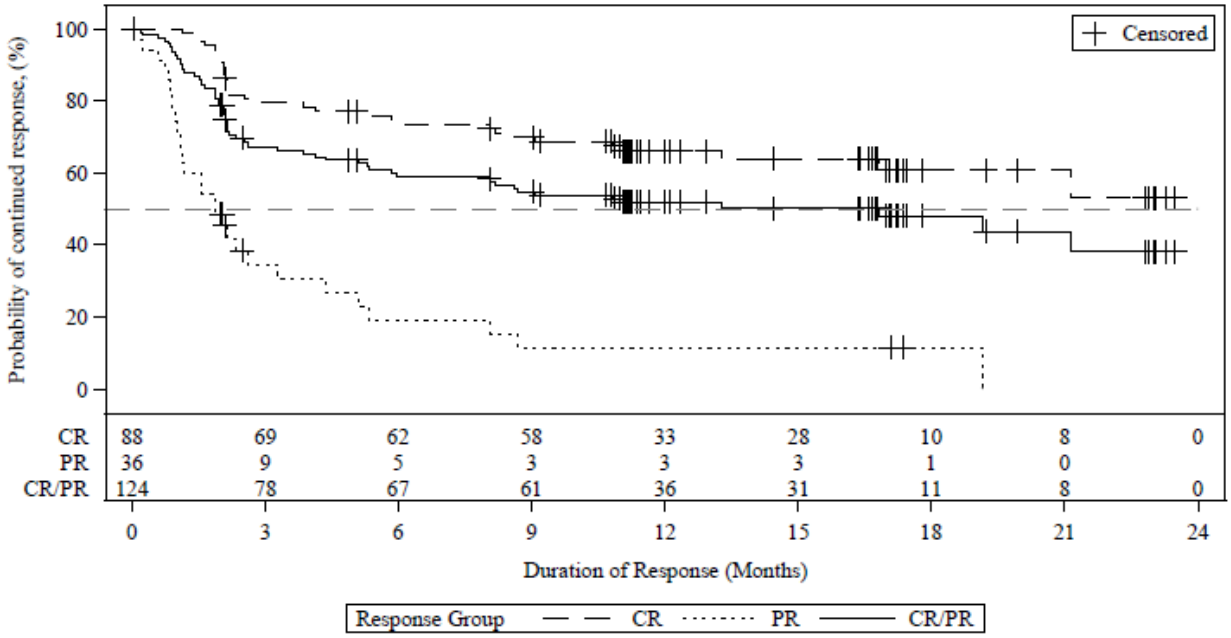
[d] Reverse KM method was used to obtain the median follow-up and its 95% CIs.

[+] Ongoing.

In the Efficacy set, the ORR results within PMBCL and FL3B were 79% (11/14 patients) and 50% (1/2 patients) respectively. CR rates were 50% for both PMBCL and FL3B.

Among patients who had a best overall response of CR, the probability of continued CR at 6 months and 12 months was 74% (95% CI: 63%-82%) and 66% (95% CI:55%-75%) respectively, post-initial response (Figure 1).

Figure 1: Duration of Response by Best Overall Response, TRANSCEND, Efficacy Set



CR = complete response; PR = partial response.
Deaths after initiation of anti-cancer treatment were considered as events

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Genotoxicity assays and carcinogenicity studies were not conducted. *In vitro* expansion studies from healthy donors and patients showed no evidence for transformation and/or immortalization and no preferential integration near genes of concern in Breyanzi T cells.

Given the nature of the product, non-clinical studies on fertility were not conducted.

17 SUPPORTING PRODUCT MONOGRAPHS

1) ACTEMRA (tocilizumab for injection, 20 mg/mL vials, 162 mg/0.9 mL pre-filled syringe), Submission Control No. 236665, Product Monograph. Hoffmann-La Roche Limited, Date of Revision: July 23, 2020.

2) Fludarabine Phosphate for Injection (Sterile Solution for Injection 25 mg/mL, 2 mL per vial), Submission Control No. 190383, Product Monograph. Teva Canada Limited. Date of Revision: March 1, 2016.

3) PROCYTOX (cyclophosphamide tablets USP: 25 mg, 50 mg; cyclophosphamide for injection: 200 mg, 500 mg, 1000 mg, 2000 mg (powder for injection) per vial), Submission Control No. 155509, Product Monograph. Baxter Corporation, Date of Revision: September 7, 2012.

4) SOLU-MEDROL (methylprednisolone sodium succinate for injection USP; 500 mg, 1 g vials), Submission Control No. 213593, Product Monograph. Pfizer Canada Inc., Date of Revision: May 9, 2018.

5) DEXAMETHASONE OMEGA UNIDOSE (dexamethasone sodium phosphate injection USP, 10 mg/mL), Control No. 154533, Prescribing Information. Omega Laboratories Limited, Date of Preparation: June 12, 2012.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

BREYANZI ®
(lisocabtagene maraleucel]

Read this carefully before you start taking **Breyanzi** (pronounced braye an' zee). This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Breyanzi**.

Serious Warnings and Precautions

Breyanzi can cause serious side effects. Sometimes, these serious side effects that are life-threatening can lead to death. The following serious side effects have been seen in people taking Breyanzi :

- Fever and chills which may be symptoms of a serious side effect called cytokine release syndrome (CRS), which can be severe or fatal. Other symptoms of CRS are difficulty breathing, dizziness or light-headedness, nausea, headache, fast heartbeat, low blood pressure or fatigue, vomiting, diarrhea, muscle pain and joint pain. Talk to your healthcare professional immediately if you have any of these symptoms.
- Neurological problems like confusion, difficulty with memory, difficulty speaking or slowed speech, difficulty understanding speech, loss of balance or coordination, disorientation, being less alert (decreased consciousness) or excessive sleepiness, loss of consciousness, delirious, fits (seizures), shaking or weakness with loss of movement on one side of the body. Talk to your healthcare professional immediately if you have any of these symptoms.

Breyanzi should only be given by an experienced healthcare professional at qualified treatment centres.

What is Breyanzi used for?

Breyanzi is used to treat adults with a type of blood cancer called lymphoma which affects lymph tissue and causes white blood cells to grow out of control. Breyanzi is used for:

- diffuse large B-cell lymphoma (DLBCL)
- primary mediastinal large B-cell lymphoma
- DLBCL arising from follicular lymphoma

It is used when at least 2 previous treatments have not worked or have stopped working.

How does Breyanzi work?

Breyanzi is a type of treatment called a ‘genetically modified cell therapy’. Breyanzi is made from your own white blood cells. Cells are taken from your blood and the white blood cells are separated out. Your white blood cells are then frozen and sent away to make Breyanzi.

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.

What are the ingredients in Breyanzi?

Medicinal ingredients: lisocabtagene maraleucel

Non-medicinal ingredients: caprylic acid, Cryostor® CS10, human albumin, magnesium chloride, N-acetyl-DL-tryptophan, potassium chloride, sodium acetate trihydrate, sodium chloride, sodium gluconate, water for injection

Breyanzi comes in the following dosage forms:

Breyanzi is a cell suspension for injection. Your doctor will check that the Breyanzi was prepared from your own blood by checking the patient identity information on the medicine labels matches your details. Breyanzi is given through a tube into a vein as a single-dose, one-time treatment.

Do not use Breyanzi if:

- you are allergic to Breyanzi or any of the other ingredients of this medicine (listed in "What are the ingredients in Breyanzi?" above). If you think you may be allergic to Breyanzi, ask your doctor for advice.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Breyanzi. Talk about any health conditions or problems you may have, including if you:

- have any lung or heart problems.
- have low blood pressure.
- have any symptoms of infection or other inflammatory condition, such as fever (100.4°F/38°C), chill, sore throat, coughing, chest pain, stomach pain, vomiting, and diarrhea. The infection will be treated before Breyanzi infusion.
- have had a stem cell transplant from another person in the last 4 months or any other organ transplant in the past. The transplanted cells can attack your body ('graft-versus-host disease'), causing symptoms such as rash, nausea, vomiting, diarrhea and bloody stools.
- notice the symptoms of your cancer are getting worse. In lymphoma, this might include unexplained fever, feeling weak, night sweats, sudden weight loss.
- had or have hepatitis B or C or HIV (human immunodeficiency virus) infection.
- had a vaccination in the previous 6 weeks or are planning to have one in the next few months.
- have any symptoms of severe allergic reactions, such as shortness of breath or trouble breathing, skin rash, swelling of the lips, tongue, or face, chest pain, feeling dizzy or faint.
- are pregnant, breast-feeding or plan to do so, 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 Breyanzi in pregnant or breast-feeding women are not known and it may harm your unborn baby or breast-fed child. You will be given a pregnancy test before treatment starts. Breyanzi should only be given if the results show you are not pregnant.
- are pregnant or think you may be pregnant after treatment with Breyanzi. Talk to your doctor immediately.
- are a man and you plan to father a child after Breyanzi treatment.

Other warnings you should know about:

- Do not drive, operate heavy machinery, or do other activities that could be dangerous if you are not mentally alert, for at least 8 weeks after you get Breyanzi. This is because the treatment can cause temporary memory and coordination problems, sleepiness, confusion, dizziness, and seizures.

• Do not donate blood, organs, tissues or cells for transplantation after Breyanzi treatment.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Breyanzi:

- Corticosteroids, chemotherapy, and other medications that can weaken your immune system. This is because these medicines may interfere with the effect of Breyanzi and may make Breyanzi less effective.
- Live vaccines: You must not be given certain vaccines called live vaccines (a type of vaccine made from weakened virus):
    - in the 6 weeks before you are given a 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 have any vaccinations.

How you will receive Breyanzi:

Giving blood to make Breyanzi from your white blood cells

- Your doctor will take some of your blood by putting a tube (catheter) in your vein. Some of your white blood cells will be separated from your blood. The rest of your blood is returned to your body. This is called 'leukapheresis' (LOO-kuh-feh-REE-sis) and can take 3 to 6 hours. This process may need to be repeated.
- Your white blood cells will then be frozen and sent away to make Breyanzi. It takes about 3-4 weeks from the time your cells are received at the manufacturing site until Breyanzi is available to be shipped back to your treatment centre, but the time may vary.
- There is a risk of manufacturing failure (10.0%). In case of a manufacturing failure, a second manufacturing of Breyanzi may be attempted. While you wait for the product to be made again, your doctor may need to prescribe additional bridging therapy. This bridging therapy may cause side effects, which could delay or prevent you from receiving 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 acetaminophen and an antihistamine medicine. This is to reduce the risk of infusion reactions and fever.

How Breyanzi is given

- Your doctor will check that the Breyanzi was prepared from your own blood by checking the patient identity information on the medicine labels matches your details.
- Breyanzi is given through a catheter (tube) into a vein (intravenous infusion). Breyanzi is given as infusions of 2 different cell types.
- You will receive infusion of one cell type, immediately followed by the other cell type. The time for infusion will vary, but the treatment usually takes less than 15 minutes for each of the 2 cell types.

After Breyanzi is given

- Stay close to the treatment centre (within 2 hours distance) where you received Breyanzi – for at least 4 weeks.

- During the first week after treatment, you will need to return to the treatment centre 2 to 3 times for monitoring.
- This is so your doctor can check that the treatment is working – and help you if you have any side effects.
- Your doctor will give you a **Patient Alert Card**. Read it carefully and follow the instructions on it.
- Always show the Patient Alert Card to the doctor or nurse when you see them or if you go to hospital.
- Your healthcare professional will want to do blood tests to follow your progress. It is important that you do have your blood tested. If you miss an appointment, call your healthcare professional as soon as possible to make another appointment.

Usual dose:

Breyanzi comes as a cell suspension in up to 4 vials of each CD8 or CD4 component. The dose contains between 60 x 10^6 to 120 × 10^6 CAR-positive T-cells. Breyanzi should be given to you as a single-dose, one-time treatment.

What are possible side effects from using Breyanzi?

These are not all the possible side effects you may have when taking Breyanzi. If you experience any side effects not listed here, tell your healthcare professional.

Very common:
• infections – fever, chills, sore throat, chest infection, cough, or any other 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'
• low levels of red blood cells, which may make you feel weak or tired.
• bleeding or bruising more easily – due to a low level of blood cells called 'platelets'
• difficulty sleeping
• confused thinking, feeling anxious
• numbness and tingling in the feet or hands
• low or high blood pressure
• cough
• feeling sick or being sick
• diarrhea or constipation
• stomach pain
• passing less urine, and dark urine
• swollen ankles, arms, legs and face.

Common:
• trouble with balancing or walking
• changes in vision
• changes in the way things taste
• stroke or mini-strokes
• convulsions or seizures (fits)
• heart weakness, causing shortness of breath and ankle swelling
• blood clots
• shortness of breath
• bleeding in your gut

• rash
• infusion reactions – such as feeling dizzy, fever, and shortness of breath.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Fever, chills or shaking, feeling tired, fast or uneven heartbeat, feeling light-headed and short of breath – may be signs of a serious problem called 'cytokine release syndrome'		✓	✓
Feeling very tired, weak and short of breath – may be signs of low red blood cell levels (anemia)		✓	
Bleeding or bruising more easily – may be signs of low levels of cells in the blood known as platelets (thrombocytopenia)		✓	
Low number of white blood cells in your blood test; you may or may not have an infection at the same time (neutropenia or febrile neutropenia)		✓	
COMMON			
Confusion, being less alert (decreased consciousness), difficulty speaking or slurred speech, shaking (tremor), feeling dizzy and headache – may be signs of problems with your nervous system (possible symptoms of neurologic problems)		✓	✓
Feeling warm, fever, chills or shivering – may be a sign of infection		✓	
Dizziness, light headedness caused by low blood pressure (hypotension)		✓	
Bleeding in your stomach, bowel or blood in the stool (gastrointestinal hemorrhage)		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

If you want more information about Breyanzi:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.bms.com/ca/en, or by calling 1-866-463-6267.

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