New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Breyanzi® (lisocabtagene maraleucel)) [Juno Therapeutics Inc., a Bristol-Myers Squibb Company]**
Dosage Formulations:	• Cell suspension for infusion • A single dose contains 50 to 110 × 10^6 CAR-positive viable T cells, consisting of CD8 and CD4 components, with each component supplied separately in single-dose vials. • More than one vial of each of the CD8 component and/or CD4 component may be needed to achieve the total dose. • Each vial contains between 6.9 × 10^6 and 322 x 10^6 CAR-positive viable T cells in 4.6 mL cell suspension (between 1.5 × 10^6 and 70 x 10^6 CAR-positive viable T cells/mL).
FDA Approval Date: **FDB File Date:**	FDA: February 5, 2021 FDB: February 14, 2021
Indication:	• The treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B. • Not indicated for the treatment of patients with primary central nervous system lymphoma.
Mechanism of Action:	• Chimeric antigen receptor (CAR) T cell immunotherapy • Breyanzi is a CD19-directed genetically modified autologous cell 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 activation and antitumor activity, while 4-1BB (CD137) signaling enhances the expansion T cell and persistence of Breyanzi. • CAR binding to CD19 expressed on the cell surface of tumor and normal B cells induces activation and proliferation of CAR T cells, release of pro-inflammatory cytokines, and cytotoxic killing of target cells.
Dose/ Administration:	• A single dose of Breyanzi contains 50 to 110 × 10^6 CAR-positive viable T cells (consisting of 1:1 CAR-positive viable T cells of the CD8 and CD4 components), with each component supplied separately in one to four single-dose vials. • Autologous use only - verify the patient's identity prior to infusion. • Pretreatment: Administer the lymphodepleting chemotherapy regimen of fludarabine 30 mg/m^2/day intravenously and cyclophosphamide 300 mg/m^2/day intravenously for 3 days. Infuse Breyanzi 2 to 7 days after completion of chemotherapy unless serious adverse events occur. • Pre-medicate with acetaminophen and diphenhydramine or another H1-antihistamine approximately 30 to 60 minutes prior to Breyanzi infusion. Avoid use of prophylactic systemic corticosteroids as they may interfere with the activity of Breyanzi. • Ensure tocilizumab (Actemra®) and emergency equipment are available prior to infusion and during the recovery period. • Once thawed and drawn into syringes, proceed with Breyanzi administration as soon as possible. The CD8 component is administered first, followed by the CD4 component. The total time from removal from frozen storage to patient administration should not exceed 2 hours. • Monitor patients at the certified healthcare facility daily for at least seven days following infusion for signs and symptoms of cytokine release syndrome (CRS) and neurologic events.

- Instruct patients to remain within proximity of the certified healthcare facility for at least four weeks following infusion.

Disease State Clinical Highlights:

- Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL), accounting for about 23% of newly diagnosed cases in the United States. Incidence of DLBCL generally increases with age, with about 50% of patients with DLBCL being 60 years of age or older.
- Follicular lymphoma (FL) grade 3B is commonly treated as DLBCL. FL is the most common indolent (slow-growing) form of NHL, accounting for just over 10 percent of all B-cell NHLs.

Drug Clinical Highlights:

- CAR-T Cell therapy is a type of immunotherapy that involves engineering a patient's own T cells to recognize and attack cancer cells.
- Safety and efficacy was evaluated in an open-label, multicenter, single-arm trial (TRANSCEND; NCT02631044):
  - Enrolled adult patients with relapsed or refractory large B-cell non-Hodgkin lymphoma after at least 2 lines of therapy.
  - Of 299 patients who underwent leukapheresis and for whom Breyanzi was manufactured, 192 patients were evaluable for efficacy.
    - The median number of prior therapies was 3 (range 1-8)
    - Diagnoses were de novo DLBCL (53%), DLBCL transformed from indolent lymphoma (25%), high-grade B-cell lymphoma (14%), primary mediastinal large B-cell lymphoma (7%), and follicular lymphoma, grade 3B (1.0%)
    - 64% of patients had disease refractory to last therapy, 53% had primary refractory disease, 37% had prior autologous and/or allogeneic hematopoietic stem cell transplant, and 2.6% had CNS involvement
  - Efficacy was based on complete response rate and duration of response as determined by an independent review committee using 2014 Lugano criteria
  - Among the complete responders, 65% had remission lasting at least 6 months and 62% had remission lasting at least 9 months

TRANSCEND; NCT02631044	
Response Rate	**Evaluable Patients (N=192)**
Overall Response Rate, n [95% CI]	141 (73%) [67%, 80%]
Complete Response Rate, n [95% CI]	104 (54%) [47%, 61%]
Partial Response Rate, n [95% CI]	37 (19%) [14%, 26%]
Duration of Response (DOR)	
Number of Responders	141
DOR (Months) Median [95% CI] Range	 16.7 [5.3, NR] 0.0+ to 23.5+
DOR if Best Response is CR (Months) Median [95% CI] Range	 NR [16.7, NR] 0.7+ to 23.5+
DOR if Best Response is PR (Months) Median [95% CI] Range	 1.4 [1.1, 2.2] 0.0+ to 22.8+

DOR=duration of response; CI=confidence interval; CR=complete response; PR=partial response; NR=not reached

- Boxed warnings:
  - Cytokine Release Syndrome (CRS):
    - CRS occurred in 46% of patients, including ≥ Grade 3 CRS in 4% of patients

	▪ One patient had fatal CRS and 2 had ongoing CRS at time of death ▪ Median time to onset was 5 days ▪ CRS resolved in 98% of patients with a median duration time of 5 days ▪ Do not administer to patients with active infections or inflammatory disorders ▪ Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids ○ Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving Breyanzi, including concurrently with CRS, after CRS resolution, or in the absence of CRS: ▪ Neurologic toxicities occurred in 35% of patients, including ≥ Grade 3 in 12% of patients ▪ Three patients had fatal neurologic toxicity and 7 had ongoing neurologic toxicity at time of death ▪ Median time to onset was 8 days ▪ Neurological toxicities resolved in 85% of patients with a median duration of 12 days ▪ Monitor after treatment and provide supportive care and/or corticosteroids as needed ○ Only available through the Breyanzi REMS Program: ▪ Certified healthcare facilities must have on-site, immediate access to tocilizumab and ensure that a minimum of two doses of tocilizumab are available for each patient for infusion within two hours after Breyanzi infusion, if needed for treatment of CRS. ▪ Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense, or administer Breyanzi are trained in the management of CRS and neurologic toxicities. • Contraindications: none • Warnings: ○ Hypersensitivity Reactions: monitor during infusion for serious hypersensitivity reactions, including anaphylaxis, that may be due to dimethyl sulfoxide (DMSO) ○ Serious Infections: monitor and treat appropriately ○ Prolonged Cytopenias: patients may exhibit Grade 3 or higher cytopenias for several weeks following infusion; monitor complete blood counts ○ Hypogammaglobulinemia: monitor and consider immunoglobulin replacement therapy ○ Secondary Malignancies: monitor life-long after treatment ○ Patients should refrain from driving or operating heavy equipment for at least 8 weeks after therapy. • Adverse Reactions (incidence ≥ 20%): fatigue, CRS, musculoskeletal pain, nausea, headache, encephalopathy, infections (pathogen unspecified), decreased appetite, diarrhea, hypotension, tachycardia, dizziness, cough, constipation, abdominal pain, vomiting, and edema
Price Per Unit (WAC):	• $410,300.00 for a one-time therapy
Therapeutic Alternatives:	• Breyanzi is the fourth CAR-T Cell Therapy to receive FDA approval and the third with an indication for DLBCL. • Breyanzi's manufacturing process gives equal numbers of CD8 and CD4 CAR cells in a 1:1 ratio by separating out the CD8 and CD4 types of T cells first and then manufacturing CAR T Cells out of them separately. Thus, when Breyanzi is administered to a patient, it is known exactly how many CD8 and CD4 T cells the patient receives. This defined mixture of CD8 and CD4 cells may be the reason for the less adverse events and toxicities seen with Breyanzi. Other CAR-T Cell products are an unknown mix of varying ratios of different types of T cells. • The manufacturer of Breyanzi is targeting a 24 day turnaround time between when the tumor cells are extracted from a patient and when the individualized treatment is ready

to administer. In comparison, Kymriah has shown a median turnaround time of 22 days, while Yescarta shows a median turnaround time of 17 days.

- The manufacturer of Breyanzi intends to focus on treatment in outpatient settings. For patients treated in an outpatient setting, the Cell Therapy 360® program has been developed, which includes a smartphone app and disposable patch that can track body temperature in real time when outside the treatment center. However, many patients still require a hospital stay after administration due to adverse events. In a study presented at the 2020 Transplantation and Cellular Therapy Meetings of the American Society for Transplantation and Cellular Therapy, about 60% to 70% of patients who were administered Breyanzi required hospitalization after administration.

CAR-T Cell Therapies	Kymriah® (tisagenlecleucel)	Yescarta® (axicabtagene ciloleucel)	Breyanzi® (lisocabtagene maraleucel)
Indications	• Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma • Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse	• Adult patients with relapsed or refractory 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, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma • Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy	• Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B
Efficacy in DLBCL	• CR: 32% • PR: 18%	• CR: 51% • PR: 21%	• CR: 54% • PR: 19%
Incidence of CRS	• 74% in DLBCL	• 94% in DLBCL	• 46%
Incidence of Neurological Toxicities	• 58% in DLBCL	• 87% in DLBCL	• 35%
Cost per infusion	$373,000.00 WAC	$399,000.00 WAC	$410,300.00 WAC
Manufacturer	Novartis	Kite Pharma, Inc.	Bristol-Myers Squibb

CR=complete response; PR=partial response

- R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) has become the standard of care for newly diagnosed DLBCL. This therapy is able to cure 2/3 of patients but the remaining patients tend to fare poorly. ISRT radiation typically follows R-CHOP.
- For relapsed and refractory DLBCL, treatment depends on whether the patient is a transplant candidate. Preferred second-line therapies include:
  - DHAP (dexamethasone, cisplatin, cytarabine) +/- rituximab
  - DHAX (dexamethasone, cytarabine, oxaliplatin) +/- rituximab
  - GDP (gemcitabine, dexamethasone, cisplatin) +/- rituximab
  - ICE (ifosfamide, carboplatin, etoposide) +/- rituximab
  - GemOx +/- rituximab
  - Polatuzumab vedotin +/- bedamustine +/- rituximab
- National Comprehensive Cancer Network (NCCN) Guidelines list 3 CAR-T therapies, (Kymriah, Yescarta, and Breyanzi) as appropriate third-line treatments for refractory and relapsed DLBCL.

Prior Authorization Approval Criteria:	**Must meet the following criteria:** Initial Therapy: • Prescribed by or in consultation with an oncologist, hematologist, or other specialist in the treated disease state • Participant aged ≥ 18 years • Participant is currently not pregnant • Documented diagnosis of relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B (ICD-10 C82.4X, C82.5X, C83.3X, C83.9X, or C85.2X) • Documentation of two or more previous lines of systemic therapy for treated diagnosis • No previous history of CAR-T cell therapy • No active infections or inflammatory disorders Continuation of Therapy: • None **Additional Provider Diagnostic/Monitoring Criteria, if desired:** • Participant has an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 (patient must be healthy enough to participate in the pre-treatment lymphodepleting chemotherapy regimen and the collection and cultivation [leukapheresis] process as well as to withstand potential cytokine release syndrome, neurologic toxicities, and prolonged cytopenias). • Breyanzi has not been studied in patients with creatinine clearance < 30 mL/min, alanine aminotransferase > 5 times the upper limit of normal, or left ventricular ejection fraction < 40%. • Screening for HBV, HCV, and HIV in accordance with clinical guidelines should be performed before collection of cells for manufacturing. • Vaccination with live virus vaccines is not recommended for at least six weeks prior to the start of lymphodepleting chemotherapy, during treatment with Breyanzi, and until immune recovery following treatment.
Implication to State Medicaid Program:	• LOE: 11/4/2029 or 8/17/2037 • All CAR-T cell therapy manufacturers have either ongoing studies or are planning studies evaluating the use of therapy in the first-line and second-line settings. • Breyanzi is also being studied in acute lymphocytic leukemia, chronic lymphocytic leukemia, central nervous system lymphoma, and mantle cell lymphoma. • Lonca (loncastuximab tesirine) is a cytotoxic anti-CD19 antibody being studied for use in relapsed or refractory DLBCL following two or more lines of prior systemic therapy. Lonca could potentially compete with the CAR-T therapies and has a PDUFA date of May 21, 2021.

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