NEW DRUG APPROVAL

Brand Name	Breyanzi®
Generic Name	lisocabtagene maraleucel
Drug Manufacturer	Bristol-Myers Squibb

New Drug Approval

FDA Approval Date: February 05, 2021

Review Designation: N/A

Type of Review: Biologics License Application (BLA): 125714

Dispensing Restriction: Direct Purchase Only

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL) in the United States and worldwide, accounting for about 22 percent of newly diagnosed cases of B-cell NHL in the United States. More than 18,000 people are diagnosed with DLBCL each year.

DLBCL can develop in the lymph nodes or in "extranodal sites" (areas outside the lymph nodes) such as the gastrointestinal tract, testes, thyroid, skin, breast, bone, brain, or essentially any organ of the body. It may be localized (in one spot) or generalized (spread throughout the body). Despite being an aggressive lymphoma, DLBCL is considered potentially curable.

Diffuse large B-cell lymphoma (DLBCL) is the most common form of NHL, accounting for about 23% of newly diagnosed cases of B-cell NHL in the United States. DLBCL occurs in both men and women, although it is slightly more common in men. DLBCL can occur in childhood, but its incidence generally increases with age (about 50% of patients with DLBCL are 60 years of age or older).

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Efficacy

TRANSCEND-NHL-001 Trial (NCT02631044): Study Design Summary	

Study Population	• Adult patients (18 years of age or older) with relapsed or refractory large B-cell lymphomas (BCLs) at 14 cancer centers in the United States
	• **Patient demographics:** Of the 192 patients in the main efficacy population, the median age was 63 years, 69% were male, and 84% were white (Breyanzi Prescribing Information)
	• **Median number of prior therapies:** 3
	• **Eastern Cooperative Oncology Group (ECOG) performance status at screening:**
	  ○ 0 (41%)
	  ○ 1 (58%)
	  ○ 2 (1.5%)
	• **Eligible histological subgroups** included DLBCL; high-grade BCL with rearrangements of MYC and either BCL2, BCL6, or both (double-hit or triple-hit lymphoma); DLBCL transformed from any indolent lymphoma; primary mediastinal BCL; and follicular lymphoma grade 3B.
	• **Key exclusion criteria:** Patients with a history of CNS disorders (such as seizures or cerebrovascular ischemia) or autoimmune disease requiring systemic immunosuppression were ineligible.

Interventions	• Patients were assigned to one of three target dose levels of liso-cel as they were sequentially tested in the trial:
	  ○ 50×10^6 CAR+ T cells (one or two doses)
	  ○ 100×10^6 CAR+ T cells
	  ○ 150×10^6 CAR+ T cells
	All groups were given a sequential infusion of two components (CD8+ and CD4+ CAR+ T cells) at equal target doses.

Endpoints	**Primary endpoints:** Adverse events, dose-limiting toxicities, and the objective response rate (assessed per Lugano criteria); endpoints were assessed by an independent review committee in the efficacy-evaluable set (comprising all patients who had confirmed PET-positive disease and received at least one dose of liso-cel).

Safety Results	• Any-grade CRS occurred in 46% (122/268) of patients using the Lee grading system • Grade ≥3 CRS occurred in 4% (11/268) of patients • 1 patient had fatal CRS and 2 patients had ongoing CRS at the time of death • The most common manifestations of CRS included fever (93%), hypotension (49%), tachycardia (39%), chills (28%) and hypoxia (21%)

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Safety Results (cont.)	• Median duration of CRS: 5 days (range, 1–30 days) • Median time to onset: 5 days (range, 1–15 days) • Any-grade neurologic toxicities (NT) occurred in 35% (95/268) of patients receiving Breyanzi • Grade ≥3 NT occurred in 12% (31/268) of patients • 3 patients had fatal neurologic toxicity and 7 had ongoing neurologic toxicity at time of death • The most common NT included encephalopathy (24%), tremor (14%), aphasia (9%), delirium (7%), headache (7%), ataxia (6%), and dizziness (6%) • Neurologic toxicities resolved in 81 of 95 patients (85%), with a median duration of 12 days (range, 1–87 days) • Median time to onset of the first event: 8 days (range, 1–46 days) • Median duration of neurologic toxicity: 15 days (range, 1–785 days) in all patients, including those with ongoing neurologic events at the time of death or at data cutoff **Serious adverse reactions** occurred in 46% of patients. The most common nonlaboratory, serious adverse reactions (>2%) were CRS, encephalopathy, sepsis, febrile neutropenia, aphasia, pneumonia, fever, hypotension, dizziness, and delirium. **Fatal adverse reactions** occurred in 4% of patients.
Efficacy Results	• Overall response rate: 73% • Complete response rate: 54% • Partial response rate: 19% • Duration of response: 16.7 months • Among the complete responders, 65% had remission lasting at least 6 months and 62% had remission lasting at least 9 months

Sources: NCT02631044, Breyanzi Prescribing Information

Safety

ADVERSE EVENTS

The most common nonlaboratory adverse reactions (incidence greater than or equal to 20%) in Breyanzi®-treated patients were fatigue, cytokine release syndrome, musculoskeletal pain, nausea, headache, encephalopathy, infections (pathogen unspecified), decreased appetite, diarrhea, hypotension, tachycardia, dizziness, cough, constipation, abdominal pain, vomiting, and edema.

WARNINGS & PRECAUTIONS

- Hypersensitivity Reactions: Monitor for hypersensitivity reactions during infusion.
- Serious Infections: Monitor patients for signs and symptoms of infection; treat appropriately.
- Prolonged Cytopenias: Patients may exhibit Grade 3 or higher cytopenias for several weeks following Breyanzi® infusion. Monitor complete blood counts.
- Hypogammaglobulinemia: Monitor and consider immunoglobulin replacement therapy.

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- Secondary Malignancies: Patients treated with Breyanzi® may develop secondary malignancies. Monitor lifelong for secondary malignancies. In the event that a secondary malignancy occurs after treatment with Breyanzi®, contact Bristol-Myers Squibb.
- Effects on Ability to Drive and Use Machines: Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery for at least 8 weeks after Breyanzi® administration.

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

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

ADULTS

For autologous use only. For intravenous use only.

- Do NOT use a leukodepleting filter.
- Administer a lymphodepleting regimen of fludarabine and cyclophosphamide before infusion of Breyanzi®.
- Verify the patient's identity prior to infusion.
- Premedicate with acetaminophen and an H1 antihistamine.
- Confirm availability of tocilizumab prior to infusion.
- Dosing of Breyanzi® is based on the number of chimeric antigen receptor (CAR)-positive viable T cells.
- The dose is 50 to 110 × 106 CAR-positive viable T cells (consisting of CD8 and CD4 components).
- Administer Breyanzi® in a certified healthcare facility

PEDIATRICS

The safety and efficacy of Breyanzi® have not been established in pediatric patients.

GERIATRICS

In clinical trials of Breyanzi®, 111 (41%) of the 268 patients in Transcend were 65 years of age or older, and 27 (10%) 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.

RENAL IMPAIRMENT

N/A

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HEPATIC IMPAIRMENT

N/A

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

- Breyanzi® is a cell suspension for infusion.
- A single dose of Breyanzi® contains 50 to 110 × 106 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 5 mL vials (3). Each mL contains 1.5 × 106 to 70 × 106 CAR-positive viable T cells.

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