GENE AND CELLULAR THERAPY - CAR-T Cell Immunotherapy

Lisocabtagene maraleucel (liso-cel, Breyanzi; Juno Therapeutics, inc., a Bristol-Myers Squibb Company**)**
FDA Approval Date: 2/5/21

AHFS PHARMACOLOGIC THERAPEUTIC CLASS
26:12 Gene Therapy; 10:00 Antineoplastic Agents
LEXI-COMP PHARMACOLOGIC THERAPEUTIC CLASS
Antineoplastic Agent, Anti-CD19; Antineoplastic Agent, CAR-T Immunotherapy; CAR-T Cell Immunotherapy; Cellular Immunotherapy, Autologous; Chimeric Antigen Receptor T-Cell Immunotherapy
NCCN CATEGORY
Category 2A

CURRENT FORMULARY STATUS WITHIN ENTERPRISE
Non-formulary

COMPARATIVE AGENTS
Tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta) for DLBCL.

AVAILABLE FORMULATIONS[1]
Suspension for intravenous infusion [contains albumin human]

INDICATIONS[12]
FDA Approved
- Treatment of relapsed or refractory large B-cell lymphoma in adults after ≥2 lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B.
    - Limitations of use: not indicated for the treatment of primary CNS lymphoma

Off-Label uses
- None

DESCRIPTION AND CLINICAL PHARMACOLOGY[13]
Liso-cel is a CD19-directed, genetically modified, autologous T-cell immunotherapy in which a patient's T-cells (obtained through leukapheresis) are reprogrammed with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing cells. The T-cells are administered as a defined composition of CD8- and CD4- positive CAR T cells to reduce variability. 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 initiates activation and antitumor activity, while 4-1BB (CD137) enhances T-cell expansion. CAR binding to CD19 receptors expressed on the cell surface of tumor and normal B cells induces activation and proliferation of CAR-T cells, and causes release of pro-inflammatory cytokines, causing cytotoxic killing of the target cells.

PHARMACODYNAMICS AND PHARMACOKINETICS[123]

Onset	Median time to first response (complete or partial response): 1 month.
Time to Peak	Median time to CAR T-cell peak expansion: 12 days.
Duration of Action	Liso-cel was present in peripheral blood for up to 2 years.
Expansion	Liso-cel exhibits an initial rapid expansion followed by a bi-exponential decline. Patients who receive tocilizumab and/or corticosteroids to manage cytokine release syndrome (CRS) and/or neurologic toxicity experienced higher ide-cel expansion levels and higher $AUC_{0-28}d$ and C_{max} compared to patients who did not.

DOSING AND ADMINISTRATION[13]

Adult

- For autologous IV use only. Confirm patient identity matches cartons, vials, and syringe labels prior to infusion.
- Ensure tocilizumab (2 doses) and emergency equipment are available prior to liso-cel infusion and during recovery period.
- Premedication - Premedicate with acetaminophen 650 mg orally and diphenhydramine 25-50 mg IV or orally ~30-60 minutes prior to liso-cel infusion to minimize risk of infusion reaction. Avoid prophylactic systemic corticosteroids as they may interfere with liso-cel activity. .
- Administer at a REMS-certified healthcare facility.

Indication	Dosing
Large B-cell lymphoma, relapsed or refractory: IV	• A treatment course of lymphodepleting chemotherapy, with fludarabine and cyclophosphamide, for 3 days, followed by liso-cel infusion 2-7 days after completion. Ensure availability of liso-cel prior to initiating lymphodepleting chemotherapy. • **Target dose: 50 to 110 x 10^6 CAR^+ viable T cells** (consisting of 1:1 CD8 and CD4 components). Actual cell counts and volumes for infusion are on the release for infusion (RFI) certificate.

Geriatric

- Refer to adult dosing.

Pediatric

- The safety and efficacy in patients under 18 years of age has not been studied.

Renal impairment

- Has not been studied - there are no dosage adjustments provided in the manufacturer's labeling.

Hepatic impairment

- Has not been studied - there are no dosage adjustments provided in the manufacturer's labeling.

LITERATURE REVIEW AND CLINICAL EFFICACY[4]

In the TRANSCEND clinical study, Breyanzi demonstrated rapid and durable remission, with low incidence of all-grade and severe cytokine release syndrome and neurological events among patients with high-risk aggressive relapsed or refractory large B-cell lymphomas. Clinically meaningful activity was noted in those with uncommon histological subtypes and patients with poor prognosis. Liso-cel reported an overall response rate (ORR) of 73%, complete response (CR) of 53%, median progression-free survival (PFS) of 6.8 months with 12-month rate of 44.1%, and median overall survival (OS) of 21.1 months with 12-month rate of 58%.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS[1,2,3]

Black Box Warnings

- Cytokine Release Syndrome (CRS)
  - Any-grade CRS was observed in 42% of patients grade 3 or worse occurred in 2%
  - Median time to onset: 5 days, median duration: 5 days
  - Tocilizumab use: 10%, glucocorticoid use: 2%
- Neurologic toxicities
  - Any grade neurotoxicity occurred in 30%, grade 3 or worse occurred in 10%
  - Median time to onset: 9 days, median duration: 11 days
- REMS program

Contraindications

There are no contraindications listed in the manufacturer's labeling.

Warnings and Precautions

- Cytopenias
  - Prolonged cytopenia's may occur for several weeks after lymphodepleting chemotherapy and liso-cel.
- Hepatitis B virus reactivation
  - Reactivation (sometimes resulting in fulminant hepatitis, hepatic failure, and death) can occur in patients treated with medication directed against B cells.
- Hypersensitivity
  - Allergic reactions may occur with liso-cel.
- Hypogammaglobulinemia and B-cell aplasia
- Infections
  - Infections occurred commonly with liso-cel; grade 3 or higher, life-threatening, or fatal infections have occurred. Infections include bacterial, viral, and fungal infections, as well as infection with unspecified pathogens. Neutropenic fever has been observed and may be concurrent with CRS.
- Secondary malignancies

ADVERSE REACTIONS[4]

Common

- Cardiovascular: Edema (21%), Hypotension (26%), Tachycardia (25%)
- Gastrointestinal: Abdominal pain (21%), Constipation (23%), Decrease in appetite (28%), Diarrhea (26%), Nausea (33%), Vomiting (21%)
- Musculoskeletal: Musculoskeletal pain (37%)
- Neurologic: Dizziness (24%), Headache (30%)
- Respiratory: Cough (23%)
- Other: Fatigue (48%), Infectious disease, Pathogen unspecified (29%)

Serious

- See "Contraindications, Warnings, and Precautions" above.
- Other
  - Neurologic: Seizure (1.1%), Tremor (16%)
  - Psychiatric: Delirium (10%)
  - Respiratory: Pneumonia (8%)
  - Infusion reaction (1.9%), Sepsis (4.5%), Tumor lysis syndrome (0.7%)

Dose Adjustments for Toxicity[13]

Cytokine Release Syndrome

CRS Grade	Tocilizumab	Corticosteroids
Grade 1: fever	If ≥72h after infusion, manage symptomatically. If <72h, consider tocilizumab 8 mg/kg IV over 1h.	If ≥72h after infusion, manage symptomatically. Consider dexamethasone 10 mg IV every 24h.
Grade 2: symptoms require and respond to moderate intervention	Administer tocilizumab 8 mg/kg IV over 1h. Repeat every 8h PRN if not responsive to IV fluids or increasing supplemental oxygen.	Consider dexamethasone 10 mg IV every 12-24h.
	If no improvement within 24h or rapid progression, repeat tocilizumab and escalate to dexamethasone to 10-20mg IV every 6-12h If no improvement within 24h or continued rapid progression, maximize dexamethasone or switch to methylprednisolone 2mg/kg IV if needed. After 2 tocilizumab doses, consider alternative immunosuppression.	
Grade 3: symptoms require and respond to aggressive intervention	Manage per grade 2.	Administer dexamethasone 10 mg IV every 12h.
	If no improvement within 24h or rapid progression, repeat tocilizumab and escalate dexamethasone to 10-20 mg IV every 6-12h. If no improvement or continued rapid progression, maximize dexamethasone or switch to methylprednisolone 2 mg/kg IV if needed. After 2 tocilizumab doses, consider alternative immunosuppression.	
Grade 4: life-threatening symptoms	Manage per grade 2.	Administer dexamethasone 20 mg IV every 6h.
	If no improvement within 24h or rapid progression, escalate tocilizumab and corticosteroid use. If no improvement or continued rapid progression, maximize dexamethasone, or switch to methylprednisolone 2 mg/kg IV if needed. After 3 tocilizumab doses, consider alternative immunosuppression.	

*Do not exceed 3 tocilizumab doses in 24 hours and a maximum total of 4 tocilizumab doses.

Neurotoxicity

Grade	Corticosteroids and Anti Seizure Medication
1	Initiate seizure prophylaxis with non-sedating anti-seizure medications (i.e Keppra).
	If ≥72h after infusion, observe. If <72h, consider dexamethasone 10 mg IV every 12-24h for 2-3 days.
2	Initiate seizure prophylaxis with non-sedating anti-seizure medications (i.e Keppra).
	Initiate dexamethasone 10 mg IV every 12h for 2-3 days (or longer if persistent). Consider taper for a total corticosteroid exposure >3 days. If no improvement after 24h or worsening of neurologic toxicity, increase dexamethasone dose and/or frequency up to a max of 20 mg IV every 6h. If no improvement after another 24h, rapidly progressing symptoms, or life-threatening complications, administer methylprednisolone (2 mg/kg IV loading dose, followed by 0.5 mg/kg IV every 6h, taper within 7

	days)
3	Initiate seizure prophylaxis with non-sedating anti-seizure medications (i.e Keppra).
	Initiate dexamethasone 10-20 mg IV every 8-12h. They are not recommended for isolated grade 3 headaches. If no improvement after 24h or worsening of neurologic toxicity, escalate to methylprednisolone (2 mg/kg IV loading dose, followed by 0.5 mg/kg IV every 6h, taper within 7 days). If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Administer methylprednisolone 1-2 g IV, repeat every 24h if needed and taper as clinically indicated. Administer cyclophosphamide 1.5g/m^2 IV.
4	Initiate seizure prophylaxis with non-sedating anti-seizure medications (i.e Keppra).
	Initiate dexamethasone 20 mg IV every 6h. If no improvement after 24h or worsening of neurologic toxicity, administer methylprednisolone (2 mg/kg IV loading dose, followed by 0.5 mg/kg IV every 6h; taper within 7 days). If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Administer methylprednisolone 1-2 g IV, repeat every 24h if needed and taper as clinically indicated. Administer cyclophosphamide 1.5 g/m^2 IV.

Other Toxicities

Toxicity	Management
Hypogammaglobulinemia (IgG <400 mg/dL)	Manage with infection precautions, antibiotic prophylaxis, and immune globulin replacement as clinically indicated.
Infection	Administer prophylactic, preemptive, and/or therapeutic antimicrobials according to standard institutional guidelines.
Neutropenic fever	Evaluate for infection and manage with broad-spectrum antibiotics, fluids, and other supportive care as clinically indicated.

RISK EVALUATION AND MITIGATION STRATEGIES[6]

BREYANZI REMS

- Breyanzi is only available under a restricted REMS program because of the serious risks of CRS and neurologic toxicities.
- Ensuring that all hospitals and associated clinics are specially certified and enrolled in the REMS program to be able to infuse Breyanzi.
- Certified facilities must have on-site immediate access to tocilizumab.
- Ensuring that those who prescribe, dispense, or administer Breyanzi are aware of how to manage the risks of CRS and neurologic toxicities and are trained on BREYANZI REMS requirements.
- Further information is available at https://www.breyanzirems.com/ or contact Bristol Myers Squibb at 1-888-423-5436.

MAJOR INTERACTIONS[1]

Drug-Drug (Risk X - Avoid Combination)

- Immunizations
    - Immunosuppressants may enhance the adverse/toxic effect of live vaccines.
    - Immunosuppressants may diminish the therapeutic effect of live vaccines.
    - Live vaccines should not be given for at least 3 months after immunosuppressants.

    - Measles, Mumps, and Rubella Virus Vaccine - immunosuppressants may enhance the adverse/toxic effects of MMR Virus Vaccine.
    - Varicella Virus Vaccine - immunosuppressants may enhance the adverse/toxic effect of Varicella Virus Vaccine.
- BCG (Intravesical) - immunosuppressants may diminish the therapeutic effect of BCG.
- Cladribine - may enhance the immunosuppressive effect of immunosuppressants.
- Natalizumab - immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased.
- Pimecrolimus - may enhance the adverse/toxic effects of immunosuppressants.
- Tacrolimus (topical) - may enhance the adver/se toxic effects of immunosuppressants.
- Talimogene Laherparepvec - immunosuppressants may enhance the adverse/toxic effects of talimogene laherparepvec. Specifically, the risk for disseminated herpetic infection may be increased.
- Upadacitinib - immunosuppressants may enhance the immunosuppressive effect of upadacitinib.

Drug-Disease
- None

MONITORING REQUIREMENTS[13]
- Screen for HBV, HCV, and HIV prior to collection of cells for manufacturing.
- Monitor CDC prior to and after administration.
- Evaluate pregnancy stats prior to use.
- Monitor immunoglobulin levels after treatment.
- Monitor for CRS and sign/symptoms of neurotoxicity during therapy and for at least 4 weeks after infusion. Monitor patients daily at the healthcare facility for at least 7 days after cell infusion.
- Monitor for signs/symptoms of infection before and after administration.
- Monitor (lifelong) for secondary malignancies.

PREGNANCY/BREASTFEEDING[13]
- Evaluate pregnancy status prior to use in patients who may become pregnant.
- The need for a duration of contraception following exposure is not known. In a clinical trial, females and males with female partners were required to use highly effective contraception for 1 year after the last dose.
- There is no evidence regarding liso-cel safety in pregnancy. Animal studies have not been conducted. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including plasma cell aplasia or hypogammaglobulinemia. Therefore, it is not recommended to use in women who are pregnant.
- It is not known if liso-cel is present in breast milk. Considerations for risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother are recommended prior to making the decision to breastfeed.

MEDICATION SAFETY ISSUES[1]
Sound/Look Alike issues
- Liso-cel may be confused with axicabtagene ciloleucel, brexucabtagene autoleucel, idecabtagene vicluecel, sipuleucel-T, tisagenlecleucel

High Alert Medication
- This medication is in a class the Institute for Safe Medication Practices (ISMP) list of drug classes that have a heightened risk of causing significant patient harm when used in error.

SPECIAL STORAGE PRECAUTIONS[13]

- Store intact vials in the vapor phase of liquid nitrogen (≤ -130°C) in a temperature-monitored system. Once removed from frozen storage, it must be completely thawed and administered within 2 hours.
- If the patient is not expected to be ready for liso-cel administration before the shipper expires, and the infusion site is qualified for onsite storage, transfer liso-cel to onsite vapor phase of liquid nitrogen storage prior to preparation; if the infusion site is not qualified for onsite storage, contact the manufacturer to arrange for return shipment.

SPECIAL HANDLING/ADMINISTRATION[13]

- Apply universal precautions for product handling.
- The CD8 and CD4 components are supplied in separate vials (keep separate).
- Flush infusion tubing with NS prior to and after each CD4 or CD8 component. Using the Y-site or port closest to the patient, administer the entire volume of CD8 component syringe at a rate of ~0.5 mL/min; if it requires more than one syringe, administer consecutively without delay. After, flush the line with NS and administer the CD4 component immediately after, then flush with NS again.
- Coordinate the timing of administration with thawing. Administer as soon as possible after syringe preparation (must be administered within 2 hours of thawing).
- Do not use a leukodepleting filter.

COST AND REIMBURSEMENT INFORMATION[2]

Cost (Estimated WAC)	$410,300 WAC
Sales Projections (Estimated)	Wide variation in analysts' expectations: 2021: $66M-$160M 2026: $1.8B
Medical/Pharmacy Benefit	Medical
Inpatient/Outpatient	Inpatient and outpatient
Reimbursement Code	Breyanzi is supplied in vials as separate frozen suspensions of each CD8 component (NDC 73153-0901-08) and CD4 component (NDC 73153-0902-04). Each CD8 and CD4 component is packed in a carton containing up to 4 vials, depending upon the concentration of the cryopreserved drug product CAR^+ viable T cells. The cartons for each CD8 and CD4 component are in an outer carton (NCD 73153-0900-01).
NOC Code Billing Guide	C9399 Unclassified drugs or biologicals (hospital outpatient use) J9999 Not otherwise classified, antineoplastic drugs

PATIENT ASSISTANCE AVAILABILITY[7]

- Cell Therapy 360 ® through Bristol Myers Squibb offers assistance programs that are designed to provide support throughout treatment and the initial post-infusion monitoring period.
- Financial support, post-treatment monitoring assistance, and 24/7 on-call assistance available
- Additional information provided at Celltherapy360.com; 1-888-805-4555.

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