GENE AND CELLULAR THERAPY - CAR-T Cell Immunotherapy

Idecabtagene vicleucel (ide-cel, bb2121, Abecma; Bristol Myers Squibb)
FDA Approval Date: 3/26/2021

AHFS PHARMACOLOGIC THERAPEUTIC CLASS[1]
26:12 - Gene Therapy; 10:00 - Antineoplastic Agents
LEXI-COMP PHARMACOLOGIC THERAPEUTIC CLASS[2]
Antineoplastic agent, Anti-BCMA; Antineoplastic agent, CAR-T Cell Immunotherapy; Cellular Immunotherapy, Autologous; Chimeric Antigen Receptor T-Cell Immunotherapy
NCCN CATEGORY[1]
Category 2A

CURRENT FORMULARY STATUS WITHIN ENTERPRISE
Formulary

COMPARATIVE AGENTS
Ciltacabtagene autoleucel, a pipeline CAR-T product by Johnson & Johnson could eventually be a competitor of Abecma.

AVAILABLE FORMULATIONS[3]
Suspension, intravenous: 50 mL, 250 mL, 500 mL

INDICATIONS[2]
FDA Approved

- Treatment of relapsed or refractory multiple myeloma (RRMM) in adults after ≥ 4 prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody

Off-Label uses

- None

DESCRIPTION AND CLINICAL PHARMACOLOGY[12]
Ide-cel is a B-cell maturation antigen (BMCA)-directed, genetically modified, autologous T-cell immunotherapy in which a patients T-cells are harvested through leukapheresis and then genetically modified via transduction ex vivo with an anti-BCMA02 chimeric antigen receptor (CAR) lentiviral vector (LVV). The CAR construct includes an anti-BCMA single chain variable fragment-targeting domain for antigen specificity, a transmembrane domain, a CD3-zeta T-cell activation domain, and a 4-1BB costimulatory domain. CD3-zeta signaling initiates activation and antitumor activity, while 4-1BB (CD137) enhances T-cell expansion. Antigen-specific activation of ide-cel results in CAR^+ T-cell proliferation, cytokine secretion, and subsequent cytolytic killing of BCMA-expressing cells once injected back into the patient.

Abecma is the first approved CAR-T cell therapy that targets the BCMA protein. There are four other CAR-T treatments available in the U.S. that are produced the same way, but they are engineered to target a protein called CD19 instead.

PHARMACODYNAMICS AND PHARMACOKINETICS[234]

Onset	Rapid decreases in tumor markers associated with clinical response, including serum levels of soluble BCMA, and bone marrow $CD138^+$ cells, as well as MRD negative responses, were observed within the first month.
Time to Peak	Peak levels of plasma cytokines, chemokines, and soluble immune mediators were observed within 14 days of infusion; these levels typically returned to baseline within 1 month.
Duration of Action	Ide-cel can persist in peripheral blood for up to 1 year after infusion.
Expansion	Ide-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. The median time to maximal expansion in peripheral blood (T_{max}) occurred 11 days.

DOSING AND ADMINISTRATION[23]

Adult

- For autologous IV use only. Confirm patient identity matches cassette and infusion bag prior to infusion.
- Delay ide-cel infusion up to 7 days for unresolved serious adverse events (pulmonary or cardiac events, or hypotension), including events due to prior chemotherapies, and for active infections or inflammatory disorders
- Ensure tocilizumab (at least 2 doses) and emergency equipment are available prior to infusion and during recovery period.
- Premedication - Premedicate with acetaminophen 650 mg orally and diphenhydramine 12.5 mg IV or 25-50 mg orally ~30-60 minutes prior to Ide-cel infusion. Avoid prophylactic dexamethasone or other systemic corticosteroids as they may interfere with ide-cel activity. Administer prophylactic antimicrobials as clinically indicated. Consider antiviral therapy to prevent viral reactivation as appropriate.
- Administer at a REMS-certified healthcare facility.

Indication	Dosing
Multiple myeloma, released or refractory - IV	• A treatment course of lymphodepleting chemotherapy, with fludarabine and cyclophosphamide, for 3 days, followed by ide-cel infusion 2 days after completion. • **Target dose: 300 to 460 x 10^6 CAR^+ viable T-cells.** • Provided as a single dose for infusion containing a suspension of CAR^+ T cells in one or more infusion bags (average: 3 infusion bags per patient)

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[1]

In the phase 2 KarMMA clinical study, Abecma demonstrated frequent and deep responses in patients with triple-class-exposed relapsed and refractory myeloma with observed toxic effects that are consistent in previous reports. Ide-cel reported an overall response rate (ORR) of 72%, complete response rate (CR) of 33%, median duration of response (DOR) of 10.7 months, a DOR of 19 months in patients with CR or sCR, median progression-free survival (PFS) of 8.8 months overall, a PFS of 20.2 months among patients with a complete response (CR) or better, and a median overall survival (OS) of 19.4 months with a 12-month rate of 78% .Results support substantial antitumor activity for ide-cel across a target dose range of 150 x 10^6 to 450 x 10^6 CAR^+ T cells, with the 450 x10^6 dose appearing more effective than other doses.

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

Black Box Warnings

- Cytokine Release Syndrome (CRS)
    - Any-grade CRS was observed in 84% of patients, grade 3-4 occurred in 5%
    - Median time to onset: 1-day, median duration: 5 days
    - Tocilizumab use: 52%, glucocorticoid use: 15%
- Neurologic Toxicities
    - Any-grade neurotoxicity occurred in 18% of patients, grade 3 occurred in 3% of patients
    - Median time to onset: 2 days, median duration: 3 days
- Hemophagocytic lymphohistiocytosis/macrophage activation syndrome
    - HLH/MAS occurred in 4% of patients
    - Median time to onset: 7 days
- Prolonged cytopenia
    - Prolonged grade 3 or 4 neutropenia occurred in 41% of patients, grade 3 or 4 thrombocytopenia occurred in 49% of patients
- REMS program

Contraindications

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

Warnings and Precautions

- Cytomegalovirus reactivation
    - Infection resulting in pneumonia and death has occurred.
- Hepatitis B virus reactivation
    - Reactivation (sometimes resulting in fulminant hepatitis, hepatic failure, and death) can occur in patients treated with medication directed against plasma cells.
- Hypersensitivity
    - Ide-cel contains dimethyl sulfoxide (DMSO), which has been associated with serious hypersensitivity reactions, including anaphylaxis.
- Hypogammaglobulinemia and plasma cell aplasia
- Infections
    - Severe, life-threatening, or fatal infections have occurred. Infections include bacterial, viral, and fungal as well as unspecified pathogens.
- Secondary malignancies

ADVERSE REACTIONS[2][5]

Common

- Cardiovascular - Edema (25%)
- Gastrointestinal - Decrease in appetite (22%), Diarrhea (35%), Nausea (29%)

- Musculoskeletal - Musculoskeletal pain (45%)
- Neurologic - Headache (23%)
- Respiratory - Cough (23%), Upper respiratory infection (34%)
- Other - Fatigue (45%), Fever (25%)

Serious

- See “Contraindications, Warnings, and Precautions” above
- Other
    - Neurologic - Aphasia (7%), Cerebral Edema, Encephalopathy (26%), Parkinsonism, Tremor (10%)
    - Psychiatric - Delirium (6%)

Dose Adjustments for Toxicity

Cytokine Release Syndrome

<table>
<tr><th>CRS Grade</th><th>Tocilizumab</th><th>Corticosteroids</th></tr>
<tr><td>Grade 1: symptomatic treatment only</td><td>If ≥72h after infusion, manage symptomatically. If <72h, consider tocilizumab 8 mg/kg IV over 1h.</td><td>Consider dexamethasone 10 mg IV every 24h.</td></tr>
<tr><td rowspan="2">Grade 2: symptoms require and respond to moderate intervention</td><td>Administer tocilizumab 8 mg/kg IV over 1h. Repeat every 8h PRN if not responsive to IV fluids or increasing supplemental oxygen.</td><td>Consider dexamethasone 10 mg IV every 12-24h.</td></tr>
<tr><td colspan="2">If no improvement within 24h or rapid progression, repeat tocilizumab and escalate dexamethasone to 20 mg IV every 6-12h.
If no improvement within 24h or continued rapid progression, switch to methylprednisolone 2 mg/kg IV, followed by methylprednisolone 0.5 mg/kg IV every 6h. After 2 tocilizumab doses, consider alternative anticytokine agents.</td></tr>
<tr><td rowspan="2">Grade 3: symptoms require and respond to aggressive intervention</td><td>Manage per grade 2.</td><td>Administer dexamethasone 10 mg IV every 12h.</td></tr>
<tr><td colspan="2">If no improvement within 24h or rapid progression, repeat tocilizumab and escalate dexamethasone to 20 mg IV every 6-12h.
If no improvement within 24h or continued rapid progression, switch to methylprednisolone 2 mg/kg IV, followed by methylprednisolone 0.5 mg/kg IV every 6h. After 2 tocilizumab doses, consider alternative anticytokine agents.</td></tr>
<tr><td rowspan="2">Grade 4: life-threatening symptoms</td><td>Manage per grade 2.</td><td>Administer dexamethasone 20 mg IV every 6h.</td></tr>
<tr><td colspan="2">After 2 tocilizumab doses, consider alternative anticytokine agents. If no improvement within 24h consider methylprednisolone (1-2 g IV, repeat every 24h PRN; taper as clinically indicated) or other anti-T cell therapies.</td></tr>
</table>

*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 the patient. 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. They are not recommended for isolated grade 2 headaches. 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.
3	Initiate seizure prophylaxis with non-sedating anti-seizure medications (i.e Keppra).
	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 1.5 g/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 1-2 g IV, repeat every 24h if needed and taper as clinically indicated. If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Administer methylprednisolone 1-2g IV, repeat every 24h if needed and taper as clinically indicated. Administer cyclophosphamide 1.5g/m^2 IV.

Other Toxicities

Toxicity	Management
Cytomegalovirus reactivation	Manage as clinically appropriate.
Cytopenia's	Manage cytopenia with myeloid growth factor and blood product transfusion support.
Hypogammaglobulinemia (IgG <400 mg/dL)	Administer IV immune globulin and manage as indicated with infection precautions and antibiotic and/ or antiviral prophylaxis.
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[36]

ABECMA REMS

- Healthcare facilities that dispense and administer Ide-cel must be enrolled and comply with the REMS requirements.
- Certified healthcare facilities must have on-site, immediate access to tocilizumab (at least 2 doses) for each patient for infusion within 2 hours, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense, or administer ide-cel are trained in the management of CRS and neurologic toxicities.
- Further information is available at www.AbecmaREMS.com or contact Bristol-Myers Squibb at 1-888-423-5436.

MAJOR INTERACTIONS[23]

Drug-Drug (Risk X - Avoid Combination)

- Immunizations
    - Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Ide-cel treatment, and until immune recovery following treatment with ide-cel. Immunization with live viral vaccines during or following Ide-cel has not been studied.
    - 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.
- Corticosteroids - avoid use of prophylactic corticosteroids.
- 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

- HIV and the lentivirus used to make ide-cel 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 ide-cel.

MONITORING REQUIREMENTS[23]

- Screen for HBV, HCV, and HIV prior to collection of cells for manufacturing.
- Monitor CBC prior to and after administration.
- Evaluate pregnancy status prior to use.
- Monitor immunoglobulin levels (IgG) after treatment.
- Monitor patients daily (for signs/symptoms of cytokine release syndrome and neurotoxicity) at the health care facility for at least 7 days after cell infusion. Patients should remain within proximity of the facility for at least 4 weeks after infusion.
- Monitor for signs/symptoms of cytomegalovirus and HBV reactivation, hypersensitivity, HLH/MAS, and secondary malignancies.

PREGNANCY/BREASTFEEDING[23]

- Verify pregnancy status prior to treatment initiation.
- There is no evidence regarding ide-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 ide-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[12]

Sound/Look Alike issues

- Ide-cel may be confused with axicabtagene ciloleucel, brexucabtagene autoleucel, lisocabtagene maraleucel, sipuleucel-T, tisagenlecleucel.

High Alert Medication

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

SPECIAL STORAGE PRECAUTIONS[23]

- Store frozen in the vapor phase of liquid nitrogen. Product is shipped in the vapor phase of a liquid nitrogen shipper. If the infusion site is qualified for onsite storage, transfer ide-cel to the onsite vapor phase of liquid nitrogen storage prior to preparation. If they are not qualified, contact the manufacturer to arrange for return shipment if the patient is not receiving infusion same-day.
- Ide-cel is stable for 2 hours at room temperature once thawed; administer within 1 hour of the start to thaw.

SPECIAL HANDLING/ADMINISTRATION[2]

- Ide-cel contains human blood cells that are genetically modified with replication-incompetent, self-inactivtating lentivrial vector. Follow universal precautions and local biosafety guidelines for handling and disposal to avoid transmission of infectious diseases.
- Before thawing, inspect the infusion bag(s) for breaches of container integrity (i.e breaks or cracks); contact the manufacturer if compromised. If >1 bag is received, thaw 1 bag at a time and do not initiate thawing of the next bag until infusion of the previous bag is complete.
- To thaw, place the bag inside a second sterile bag and thaw at ~37°Cusing an appropriate thaw device or water bath) until there is no visible ice in the infusion bag.
- Gently mix the bag contents to disperse cellular material clumps. If visible clumps remain, continue to gently mix the contents.
- Do not wash, spin down, and/or resuspend in new media prior to infusion.
- Prime tubing set with NS prior to infusion. Infuse Ide-cel by gravity infusion within 1 hour after the start of thaw. After the entire contents have been infused, rinse tubing with 30-60 mL NS to ensure all product was delivered.
- Do not use a leukodepletion filter. A central line may be used for administration.

COST AND REIMBURSEMENT INFORMATION[1]

Cost (Estimated WAC)	$419,500
Sales Projections (Estimated)	Analysts are predicting sales to be $103 million in 2021, $328 million in 2022, growing to $1.1 billion in 2025.
Medical/Pharmacy Benefit	Medical
Inpatient/Outpatient	Inpatient and outpatient
Reimbursement Code	50 mL infusion bag and metal cassette [NDC 59572-0515-01] 250 mL infusion bag and metal cassette [NDC 59572-0515-02] 500 mL infusion bag and metal cassette [NDC 59572-0515-03]
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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