Abecma™
(idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

ABECMA® REMS Training Program

FOR TRAINING PURPOSES ONLY.

Bristol Myers Squibb™

This educational module contains information regarding selected ABECMA-associated adverse reactions of cytokine release syndrome (CRS) and neurologic toxicities. These are not all of the adverse reactions associated with ABECMA. Please refer to the ABECMA Prescribing Information and Medication Guide for more information.

Indication

ABECMA is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

Please see full Prescribing Information, including BOXED WARNINGS and Medication Guide.

Abecma™ (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

ABECMA REMS Overview

Abecma™
(idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

About ABECMA REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program to manage known or potential risks associated with a drug and is required by the United States (US) Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks. ABECMA is only available under a restricted program called ABECMA REMS because of the serious risks of CRS and neurologic toxicities.

The goals of the ABECMA REMS are to mitigate the risks of CRS and neurologic toxicities by:

- Ensuring that hospitals and their associated clinic(s) that dispense ABECMA are specially certified and have on-site, immediate access to tocilizumab.
- Ensuring that those who prescribe, dispense, or administer ABECMA are aware of how to manage the risks of CRS and neurologic toxicities.

Abecma™ (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

Certification of Hospitals and Their Associated Clinic(s)

To become certified to dispense ABECMA, hospitals and their associated clinic(s) must:

1. Designate an authorized representative (AR) to carry out the certification process by completing and submitting the **Hospital Enrollment Form** on behalf of the hospital and its associated clinic(s).
2. Ensure the AR oversees implementation and compliance with ABECMA REMS requirements.
3. Administer ABECMA only after verifying that a minimum of 2 doses of tocilizumab are available on-site for each patient and ready for immediate administration (within 2 hours of ABECMA infusion).
4. Ensure that if the hospital or its associated clinic(s) designate a replacement AR, the replacement AR must take the **Training Program**, complete the **Knowledge Assessment**, and complete and submit a new **Hospital Enrollment Form**.

Certification of Hospitals and Their Associated Clinic(s) (cont'd)

5. Maintain documentation of all processes and procedures for the ABECMA REMS and provide documentation upon request to Celgene or to a third party acting on behalf of Celgene. Celgene Corporation is a Bristol-Myers Squibb Company.
6. Comply with audits by Celgene or a third party acting on behalf of Celgene to ensure that all training, processes, and procedures are in place and are being followed for the ABECMA REMS.

Certification of Hospitals and Their Associated Clinic(s) (cont'd)

7. Report any serious adverse events suggestive of CRS or neurologic toxicities to Celgene Corporation at www.bms.com or 1-888-805-4555, or to the FDA at www.fda.gov/medwatch or by calling 1-800-FDA-1088.
   - For the purpose of this REMS, serious adverse event is defined as any adverse experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Identifying an Authorized Representative

The AR responsible for the hospital and its associated clinic(s) must have capacity to oversee implementation of, and compliance with, the ABECMA REMS by:

1. Ensuring that all relevant staff are trained, complete the **Knowledge Assessment**, and maintain records.
2. Having the ability to ensure that processes and procedures have been established and are being followed.
3. Having the ability to comply with audits carried out by Celgene.

It is not required that the AR be a healthcare provider.

Responsibilities of the ABECMA REMS Authorized Representative

To successfully complete ABECMA REMS certification, the designated AR must:

- Complete the ABECMA REMS Training Program (live in-person, via webcast or online), which includes review of:
  - REMS **Training Program**
  - REMS **Adverse Reaction Management Guide**
- Oversee implementation and compliance with ABECMA REMS requirements on behalf of hospitals and their associated clinic(s).
- Submit a successfully completed ABECMA REMS **Knowledge Assessment** to Celgene online at www.AbecmaREMS.com, via email to REMSCallCenter@bms.com, or by fax to 1-855-496-8607.
- Submit a successfully completed ABECMA REMS **Hospital Enrollment Form** to Celgene online at www.AbecmaREMS.com, via email to REMSCallCenter@bms.com, or by fax to 1-855-496-8607.

Abecma™ (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

Responsibilities of the ABECMA REMS Authorized Representative (cont'd)

Before administering ABECMA, establish processes and procedures that are subject to monitoring by Celgene or a third party acting on behalf of Celgene to help ensure the following:

- All relevant staff involved in prescribing, dispensing, or administering of ABECMA are trained on the REMS requirements using the **Training Program**, and successfully complete and submit the **Knowledge Assessment**, and records are maintained of staff training (including a retraining process if ABECMA has not been dispensed at least once annually from the date of certification in the ABECMA REMS).
- Prior to infusing ABECMA, put processes and procedures in place to verify a minimum of 2 doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours of ABECMA infusion).
- Prior to infusing ABECMA, provide patients with the **Patient Wallet Card**.

Completion of the ABECMA REMS Training Program and Knowledge Assessment

The following individuals are recommended to complete the ABECMA REMS **Training Program**, **Adverse Reaction Management Guide**, and the **Knowledge Assessment**:

- Individuals involved in prescribing, dispensing, or administering ABECMA.
- Individuals who will be the AR or may complete tasks on behalf of the AR.
- Individuals who may discuss ABECMA REMS education with patients or provide a **Patient Wallet Card** to a patient.
- Individuals involved in the verification, dispensing, and administration of tocilizumab.
- Individuals who may be responsible for reporting adverse events per the REMS program to the FDA or to the manufacturer.

Note: Celgene recognizes that the assignment of REMS activities may be made to different personnel in each healthcare facility. Each healthcare facility should independently assess REMS training needs to ensure that appropriate personnel are trained.

Serious Risks Associated With ABECMA

Abecma™
(idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

Serious Risks Associated With ABECMA

WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, HLH/MAS, AND PROLONGED CYTOPENIA

See full Prescribing Information for complete boxed warning.

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients following treatment with ABECMA. Do not administer ABECMA to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.**
- **Neurologic toxicities, which may be severe or life-threatening, occurred following treatment with ABECMA, including concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with ABECMA. Provide supportive care and/or corticosteroids as needed.**
- **Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS), including fatal and life-threatening reactions, occurred in patients following treatment with ABECMA. HLH/MAS can occur with CRS or neurologic toxicities.**
- **Prolonged Cytopenia with bleeding and infection, including fatal outcomes following stem cell transplantation for hematopoietic recovery, occurred following treatment with ABECMA.**
- **ABECMA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ABECMA REMS.**

Abecma™ (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

Management of Cytokine Release Syndrome

Abecma™
(idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

Cytokine Release Syndrome

- CRS, including fatal or life-threatening reactions, occurred following treatment with ABECMA.
- The information in this section is based on data from the KarMMa study, a clinical trial in which 127 patients with relapsed/refractory multiple myeloma received ABECMA across a dose range of 150 to 518 x 10^6 CAR-positive T cells.
  - CRS occurred in 85% (108/127) of patients receiving ABECMA.
  - Grade 3 or higher CRS (Lee grading system[1]) occurred in 9% (12/127) of patients, with Grade 5 CRS reported in one (0.8%) patient.
  - Overall rate of CRS was 79%, and rate of Grade 2 CRS was 23% in patients treated in 300 x 10^6 CAR-positive T cells dose cohort (dose ranging from 277 to 339 x 10^6 CAR-positive T cells). For patients treated in 450 x 10^6 CAR-positive T cells dose cohort (dose range 447 to 518 x 10^6 CAR-positive T cells), the overall rate of CRS was 96% and rate of Grade 2 CRS was 40%. Rate of Grade 3 or higher CRS was similar across the dose range.
  - The median time-to-onset of CRS, any grade, was 1 day (range: 1 to 23 days).
  - The median duration of CRS was 7 days (range: 1 to 63 days) in all patients, including the patient who died. The median duration of CRS for the 450 x 10^6 CAR-positive T cells dose cohort was 7 days (range: 1 to 63 days), and was 6 days (range: 2 to 28 days) for the 300 x 10^6 CAR-positive T cells dose cohort.
  - 68 of 127 (54%) patients received tocilizumab; 35% (45/127) received a single dose while 18% (23/127) received more than 1 dose of tocilizumab. Overall, across the dose levels, 15% (19/127) of patients received at least 1 dose of corticosteroids for treatment of CRS. All patients that received corticosteroids for CRS received tocilizumab.
  - In the 450 x 10^6 CAR-positive T cells dose cohort, 68% (36/53) of patients received tocilizumab and 23% (12/53) received at least 1 dose of corticosteroids for treatment of CRS. This was higher than the tocilizumab use of 44% (31/70) and corticosteroid use of 10% (7/70) at the 300 x 10^6 CAR-positive T cells dose cohort.

Reference: 1. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124:188-195.

Signs and Symptoms of CRS

- CRS is a non–antigen-specific toxicity that occurs as a result of high-level immune activation.[1]
- Clinical symptoms and severity of CRS are highly variable, ranging from mild flu-like symptoms to multiorgan failure. Fever is a hallmark of CRS.
- Management can be complicated by concurrent conditions.
- Key manifestations of CRS is based on data from 127 patients with relapsed and refractory multiple myeloma receiving ABECMA who had received at least 3 prior lines of antimyeloma therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

Key Manifestations of CRS Observed in KarMMa

Pyrexia	98%	Hypoxia	20%
Hypotension	41%	Fatigue	12%
Tachycardia	35%	Headache	10%
Chills	31%		

Reference: 1. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124:188-195.

Abecma™ (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

Managing CRS

- Instruct patients to remain within 2 hours of the REMS-certified healthcare facility for at least 4 weeks following infusion.
- Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time.
- Monitor patients at least daily for 7 days following ABECMA infusion at the REMS-certified healthcare facility for signs and symptoms of CRS.
- Monitor patients for signs or symptoms of CRS for at least 4 weeks after infusion.
- Identify CRS based on clinical presentation.
- Evaluate for and treat other causes of fever, hypoxia, and hypotension.
- If CRS is suspected, initiate symptomatic treatment with supportive care, tocilizumab, or tocilizumab and/or corticosteroids, according to the management recommendations on slides 21-22.
- 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 severe or life-threatening CRS, consider intensive care unit level monitoring and supportive therapy.
- For CRS refractory to first line interventions such as tocilizumab or tocilizumab and corticosteroids, consider alternate treatment options (i.e., higher corticosteroid dose, alternative anti-cytokine agents, anti-T cell therapies). Refractory CRS is characterized by fevers, end-organ toxicity (e.g., hypoxia, hypotension) not improving within 12 hours of first line interventions, or development of hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS).
- If concurrent neurologic toxicity is suspected during CRS, administer:
  - Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades on slides 21-22 and 27-28
  - Tocilizumab according to the CRS grade on slides 21-22
  - Antiseizure medication according to the neurologic toxicity grade on slides 27-28

Abecma™ (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

HLH/MAS

- HLH/MAS occurred in 4% (5/127) of the patients receiving ABECMA.
- One patient treated in the 300 x 10^6 CAR-positive T cells dose cohort developed fatal multi-organ HLH/MAS with CRS. In another patient with fatal bronchopulmonary aspergillosis treated in the 450 x 10^6 CAR-positive T cells dose cohort, HLH/MAS was contributory to the fatal outcome.
- Three cases of Grade 2 HLH/MAS resolved.
- All events of HLH/MAS had an onset within 10 days of receiving ABECMA, with a median onset of 7 days (range: 4 to 9 days).
- All cases of HLH/MAS occurred in the setting of ongoing or worsening CRS. Two patients with HLH/MAS had overlapping neurotoxicity.
- Manifestations of HLH/MAS may include hypotension, hypoxia, multiple organ dysfunction, renal dysfunction, and cytopenia.
- Consider HLH/MAS in patients with progressive or refractory CRS despite treatment.
- Manage HLH/MAS per institutional guidelines.

HLH/MAS=hemophagocytic lymphohistiocytosis/macrophage activation syndrome.

Lee Criteria[1] for CRS Grading

- CRS grading is based on Lee Criteria, shown in the table below.
- Final grading should be done after reviewing all of the reported symptoms associated with CRS.

	Symptoms/Signs	CRS Grade 1 (mild)	CRS Grade 2 (moderate)	CRS Grade 3 (severe)	CRS Grade 4 (life-threatening)
			CRS grade is defined by the **most severe of the symptoms listed below,** excluding fever (i.e., SBP, oxygen requirement, and organ toxicity)		
Vital signs	**Fever**	Yes	Any	Any	Any
	Systolic blood pressure (SBP) ≤90 mmHg	N/A	Responds to IV fluids or single low-dose vasopressor	Needs high-dose or multiple vasopressors	Life-threatening
	Need for oxygen to reach oxygen saturation (SaO_2) >90%	N/A	Fraction of inspired oxygen (FiO_2) <40%	FiO_2 ≥40%	Needs ventilator support
Organ toxicity		N/A	Grade 2	Grade 3 or transaminitis Grade 4	Grade 4 (excluding transaminitis)

FiO_2=fraction of inspired oxygen; IV=intravenous; SaO_2=oxygen saturation.

Reference: 1. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124:188-195.

Abecma™ (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

ABECMA CRS Grading and Management Guidance

CRS Grade[1]	Tocilizumab*	Corticosteroids†
Grade 1		
Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	If onset 72 hours or more after infusion, treat symptomatically. If onset less than 72 hours after infusion, consider tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg).	Consider dexamethasone 10 mg IV every 24 hours.
Grade 2		
Symptoms require and respond to moderate intervention. 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.	Consider dexamethasone 10 mg IV every 12 to 24 hours.
	If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg IV every 6 to 12 hours). If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg followed by 2 mg/kg divided 4 times per day. After 2 doses of tocilizumab, consider alternative anti-cytokine agents. Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.	

IV=intravenous; FiO_2=fraction of inspired oxygen.
*Refer to tocilizumab Prescribing Information for details.
†If corticosteroids are initiated, continue corticosteroids for at least 3 doses, and taper over a maximum of 7 days.
Reference: 1. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124:188-195.

Abecma™ (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

ABECMA CRS Grading and Management Guidance (cont'd)

CRS Grade[1]	Tocilizumab*	Corticosteroids†
Grade 3		
Symptoms require and respond to aggressive intervention.	Per Grade 2.	Administer dexamethasone 10 mg IV every 12 hours.
Fever, oxygen requirement greater than or equal to 40% FiO_2, or hypotension requiring high-dose or multiple vasopressors, or Grade 3 organ toxicity, or Grade 4 transaminitis.	If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg IV every 6 to 12 hours). If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg followed by 2 mg/kg divided 4 times per day. After 2 doses of tocilizumab, consider alternative anti-cytokine agents. Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.	
Grade 4		
Life-threatening symptoms.	Per Grade 2.	Administer dexamethasone 20 mg IV every 6 hours.
Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD), or Grade 4 organ toxicity (excluding transaminitis).	After 2 doses of tocilizumab, consider alternative anti-cytokine agents. Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total. If no improvement within 24 hours, consider methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated) or other anti-T cell therapies.	

IV=intravenous; FiO_2=fraction of inspired oxygen.
*Refer to tocilizumab Prescribing Information for details.
†If corticosteroids are initiated, continue corticosteroids for at least 3 doses, and taper over a maximum of 7 days.
Reference: 1. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124:188-195.

Abecma™ (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

Management of Neurologic Toxicities

Abecma™
(idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

Clinical Presentation of Neurologic Toxicities

- Neurologic toxicities, which may be severe or life-threatening, have occurred following treatment with ABECMA, including concurrently with CRS, after CRS resolution, or in the absence of CRS.
- Symptoms are variable, and generally occur as CRS is resolving or after CRS resolves. However, some experience neurologic toxicities in the absence of CRS.
- The information in this section is based on data from the KarMMa study, a clinical trial in which 127 patients with relapsed/refractory multiple myeloma received ABECMA across a dose range of 150 to 518 x 10^6 CAR-positive T cells:
  - CAR T cell-associated neurotoxicity occurred in 28% (36/127) of patients receiving ABECMA, including Grade 3 in 4% (5/127) of patients.
  - One patient had ongoing Grade 2 neurotoxicity at the time of death. Two patients had ongoing Grade 1 tremor at the time of data cutoff.
  - The median time to onset of neurotoxicity was 2 days (range: 1 to 42 days).
  - CAR T cell-associated neurotoxicity resolved in 33 of 36 (92%). For patients who experienced neurotoxicity including three patients with ongoing neurotoxicity, the median duration of CAR T cell-associated neurotoxicity was 6 days (range: 1 to 578 days). Neurotoxicity resolved in 33 patients and median time to resolution was 5 days (range 1 to 61 days).
  - Thirty-four patients with neurotoxicity had CRS. The onset of neurotoxicity during CRS was observed in 29 patients, before the onset of CRS in three patients, and after the CRS event in two patients.
- The most frequently reported (greater than or equal to 5%) manifestations of CAR T cell-associated neurotoxicity include encephalopathy (20%), tremor (9%), aphasia (7%), and delirium (6%).

Abecma™ (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

Management of Neurologic Toxicities

- Counsel patients to seek immediate medical attention should signs and symptoms of neurologic toxicity occur at any time.
- Monitor patients at least daily for 7 days following ABECMA infusion at the REMS-certified healthcare facility for signs and symptoms of neurologic toxicities. Rule out other causes of neurologic symptoms.
- Monitor patients for signs or symptoms of neurologic toxicities for at least 4 weeks after infusion and treat promptly. Provide supportive care and/or corticosteroids as needed.
- Rule out other causes of neurologic signs or symptoms.
- If neurologic toxicity is suspected, manage according to the recommendations on slides 27-28.
- If concurrent CRS is suspected during the neurologic toxicity event, administer:
  - Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades on slides 21-22 and 27-28
  - Tocilizumab according to CRS grade on slides 21-22
  - Antiseizure medication according to neurologic toxicity grade on slides 27-28
- Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities.

CTCAE 4.03 Grading of Individual Neurologic Symptoms of Neurologic Toxicities Used to Determine Overall Grade of Neurologic Toxicities

Adverse event term/ Neurotoxicity domain[2]	Grade 1	Grade 2	Grade 3	Grade 4
Cerebral edema	N/A	N/A	N/A	Life-threatening consequences; urgent intervention indicated
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences
Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write, communicate intelligibly	N/A
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	N/A
Seizure	Brief partial seizure and no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening consequences; urgent intervention indicated
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	N/A

ADL=activities of daily living; CTCAE=Common Terminology Criteria for Adverse Events.

Reference: 2. National Cancer Institute, National Institutes of Health, US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. Bethesda, MD: National Institutes of Health; 2009. Revised June 2010. NIH publication 09-5410.

Abecma™ (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

Neurologic Toxicity Grading and Management Guidance

NT Grade[2]	Corticosteroids and Antiseizure Medications
Grade 1	
	Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. If 72 hours or more after infusion, observe patient. If less than 72 hours after infusion, consider dexamethasone 10 mg IV every 12 to 24 hours for 2 to 3 days.
Grade 2	
	Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Start dexamethasone 10 mg IV every 12 hours for 2 to 3 days, or longer for persistent symptoms. Consider taper for a total steroid exposure of greater than 3 days. Steroids are not recommended for isolated Grade 2 headaches. 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.

IV=intravenous; NT=neurologic toxicity.

Reference: 2. National Cancer Institute, National Institutes of Health, US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. Bethesda, MD: National Institutes of Health; 2009. Revised June 2010. NIH publication 09-5410.

Abecma™ (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

Neurologic Toxicity Grading and Management Guidance (cont'd)

NT Grade[2]	Corticosteroids and Antiseizure Medications
Grade 3	
	Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Start dexamethasone 10 to 20 mg IV every 6 to 12 hours. Steroids are not recommended for isolated Grade 3 headaches. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to methylprednisolone (2 mg/kg loading dose, followed by 2 mg/kg divided into 4 times a day; taper within 7 days). 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 g/m^2.
Grade 4	
	Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis. Start dexamethasone 20 mg IV every 6 hours. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to high-dose methylprednisolone (1-2 g, repeated every 24 hours if needed; taper as clinically indicated). 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 g/m^2.

IV=intravenous; NT=neurologic toxicity.

Reference: 2. National Cancer Institute, National Institutes of Health, US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. Bethesda, MD: National Institutes of Health; 2009. Revised June 2010. NIH publication 09-5410.

Abecma™ (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

Prolonged Cytopenia

Abecma™
(idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

Prolonged Cytopenia

- Prolonged cytopenia is defined as Grade 3 or 4 neutropenia or thrombocytopenia that has not resolved by Month 1 following ABECMA infusion.
- In the KarMMa study, 3 patients (3/127) underwent stem cell therapy for hematopoietic reconstitution due to prolonged cytopenia. Two patients underwent autologous and 1 patient underwent allogeneic stem cell transplant.
- Two of the 3 patients died from complications of prolonged cytopenia, which occurred in the setting of ongoing or prior severe CRS or HLH/MAS (lower GI bleeding and bronchopulmonary aspergillosis). The third patient recovered from neutropenia after autologous stem cell transplant.
- 41% (52/127) of patients experienced prolonged neutropenia and 49% (62/127) developed prolonged thrombocytopenia after ABECMA infusion.
- The rate of prolonged neutropenia was 49% in the 450 x 10^6 CAR-positive T cells dose cohort and 34% in the 300 x 10^6 CAR-positive T cells dose cohort.
- In 83% (43/52) of patients who recovered from Grade 3 or 4 neutropenia after Month 1, the median time to recovery from ABECMA infusion was 1.9 months. In 65% (40/62) of patients who recovered from Grade 3 or 4 thrombocytopenia, the median time to recovery was 2.1 months.
- Median time to cytopenia recovery was similar across the 300 x 10^6 and 450 x 10^6 CAR-positive T cells dose cohorts.
- Monitor and provide supportive care per institutional guidelines for prolonged cytopenia.

ABECMA Infusion Delays

Delay the infusion of ABECMA for up to 7 days if a patient has any of the following conditions:

- Unresolved serious adverse events (especially pulmonary events, cardiac events, or hypotension) including those after preceding chemotherapies
- Active infections or inflammatory disorders

Reporting Adverse Events

- Reporting suspected adverse events after administration of ABECMA is important and allows continued monitoring of the risk/benefit balance of therapy.
- Report any serious adverse events suggestive of CRS or neurologic toxicities to Celgene Corporation at www.bms.com or 1-888-805-4555, or FDA at www.fda.gov/medwatch or by calling 1-800-FDA-1088.
  - For the purpose of this REMS, serious adverse event is defined as any adverse experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

ABECMA REMS Program Materials

- ABECMA REMS Training Program
- ABECMA REMS Knowledge Assessment
- ABECMA REMS Hospital Enrollment Form
- ABECMA REMS Patient Wallet Card
- ABECMA REMS Adverse Reaction Management Guide
- ABECMA REMS Program Website www.AbecmaREMS.com

Patient Counseling

Abecma™
(idecabtagene vicleucel) SUSPENSION FOR IV INFUSION

Patient Counseling

- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Talk to the patient about the risks of CRS and neurologic toxicities and advise patients to seek immediate medical care for any of the following:
  - CRS: fever, hypotension, tachycardia, chills, hypoxia, headache, and fatigue.
  - Neurologic toxicities: signs or symptoms associated with neurologic events including encephalopathy, confusion, seizures, tremor, aphasia, delirium, and somnolence.
  - Patients treated with ABECMA may develop secondary malignancies. In the event that a secondary malignancy occurs, advise patients to contact Bristol Myers Squibb at 1-888-805-4555 for reporting and to obtain instructions on collection of patient samples for testing of secondary malignancy of T cell origin.
- Prior to infusion, provide the patient with the **Patient Wallet Card**.
- Advise patients for the need to:
  - Remain within 2 hours of the REMS-certified healthcare facility for at least 4 weeks following infusion and return to the REMS-certified healthcare facility if they need medical care.
  - Refrain from driving or operating heavy or potentially dangerous machines until at least 8 weeks after ABECMA administration.

To learn more about the ABECMA REMS, please visit www.AbecmaREMS.com or call 1-888-423-5436.

Bristol Myers Squibb™

Abecma™ (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION