Guidance on Managing Cytokine Release Syndrome (CRS)

Identify CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 1.

Patients who experience CRS should be closely monitored for cardiac and organ function until resolution of symptoms. Consider antiseizure prophylaxis with levetiracetam in patients who experience CRS.

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 in Tables 1 and 2
- Tocilizumab according to the CRS grade in Table 1
- Antiseizure medication according to the neurologic toxicity in Table 2

Please see Table 1: CRS Grading and Management Guidance on the next page.
### Table 1: CRS Grading and Management Guidance

<table>
<thead>
<tr>
<th>CRS Grade*</th>
<th>Tocilizumab†</th>
<th>Corticosteroids‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td>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).</td>
<td>Consider dexamethasone 10 mg IV every 24 hours.</td>
</tr>
<tr>
<td>Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).</td>
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<tr>
<td><strong>Grade 2</strong></td>
<td>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.</td>
<td>Consider dexamethasone 10 mg IV every 12 to 24 hours.</td>
</tr>
<tr>
<td>Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO\textsubscript{2} or hypotension responsive to fluids, or low dose of 1 vasopressor, or Grade 2 organ toxicity.</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td>Per Grade 2.</td>
<td>Administer dexamethasone 10 mg IV every 12 hours.</td>
</tr>
<tr>
<td>Symptoms require and respond to aggressive intervention. Fever, oxygen requirement greater than or equal to 40% FiO\textsubscript{2}, or hypotension requiring high-dose or multiple vasopressors, or Grade 3 organ toxicity or Grade 4 transaminitis.</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td><strong>Grade 4</strong></td>
<td>Per Grade 2.</td>
<td>Administer dexamethasone 20 mg IV every 6 hours.</td>
</tr>
<tr>
<td>Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD), or Grade 4 organ toxicity (excluding transaminitis).</td>
<td>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.</td>
<td></td>
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</tbody>
</table>

FiO\textsubscript{2}=fraction of inspired oxygen; IV=intravenous.

*Lee criteria for grading CRS (Lee et al, 2014).† 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.
ABECMA® Adverse Reaction Management Guide

Guidance on Managing Neurologic Toxicities

Monitor patients for signs or symptoms of neurologic toxicities (Table 2). Rule out other causes of neurologic signs or symptoms. Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities. If neurologic toxicity is suspected, manage according to the recommendations in Table 2.

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 in Tables 1 and 2
- Tocilizumab according to CRS grade in Table 1
- Antiseizure medication according to neurologic toxicity in Table 2

Table 2: Neurologic Toxicities Grading and Management Guidance

<table>
<thead>
<tr>
<th>Neurologic Toxicity Grade*</th>
<th>Corticosteroids and Antiseizure Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td>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/m².</td>
</tr>
<tr>
<td><strong>Grade 4</strong></td>
<td>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/m².</td>
</tr>
</tbody>
</table>

*NCI CTCAE criteria for grading neurologic toxicities version 4.03.


Please see full Prescribing Information, including Boxed Warning and Medication Guide.
**Boxed Warning**

**CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, HLH/MASS, AND PROLONGED CYTOPENIA**

- 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/MASS), including fatal and life-threatening reactions, occurred in patients following treatment with ABECMA. HLH/MASS 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.

**About ABECMA REMS**

ABECMA is a drug safety program to manage known or potential risks associated with a drug and is required by the United States 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 ABECMA REMS are to mitigate the risks of CRS and neurologic toxicities by:

1. Ensuring that hospitals and their associated clinics that dispense ABECMA are specially certified and have on-site reimbursement access to tocilizumab.
2. Ensuring that those who prescribe, dispense, or administer ABECMA are aware of how to manage the risks of CRS and neurologic toxicities.

**ABECMA REMS Requirements**

All hospitals and their associated clinics must be certified and enrolled in the ABECMA REMS to be able to dispense ABECMA.

All relevant staff involved in the prescribing, dispensing, or administering of ABECMA are trained in ABECMA REMS requirements, and must successfully complete the Knowledge Assessment and submit it to the REMS Program.

**Hospital and Associated Clinic Enrollment Instructions**

To become certified to dispense ABECMA, hospitals and their associated clinics must designate an authorized representative (AR) to complete REMS requirements, and enroll in ABECMA REMS. The AR must:

1. Complete and submit ABECMA REMS Training Program (five increments, one mandatory, one optional), which includes review of:
   - REUS Training Program
   - REUS Advisory Reaction Management Guide

2. Successfully complete the Knowledge Assessment and submit it to the REMS Program.

3. Oversee implementation and compliance with ABECMA REMS requirements to:
   - Ensure that 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.
   - Put processes and procedures in place to ensure that staff involved in the prescribing, dispensing, or administering of ABECMA are trained on ABECMA REMS 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).
   - Prior to infusing ABECMA, provide patients with the Patient Wallet Card and instruct patients to remain within 2 hours of the certified healthcare facility for at least 4 weeks following ABECMA infusions.
   - Ensure that upon the hospital and its associated clinics designate an AR, the AR must complete the Training Program, successfully complete the Knowledge Assessment, and complete and submit a new Hospital Enrollment Form.

4. Submit a completed Hospital Enrollment Form.

Report suspected adverse reactions to Celgene Corporation, a Bristol-Myers Squibb Company, at www.bms.com or 1-800-805-4355 or by the FDA at www.fda.gov/medwatch or by calling 1-800-332-1088.

**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.