Up Close with Teclistamab

This section provides an overview of teclistamab-cqyv (TECVAYLI®).

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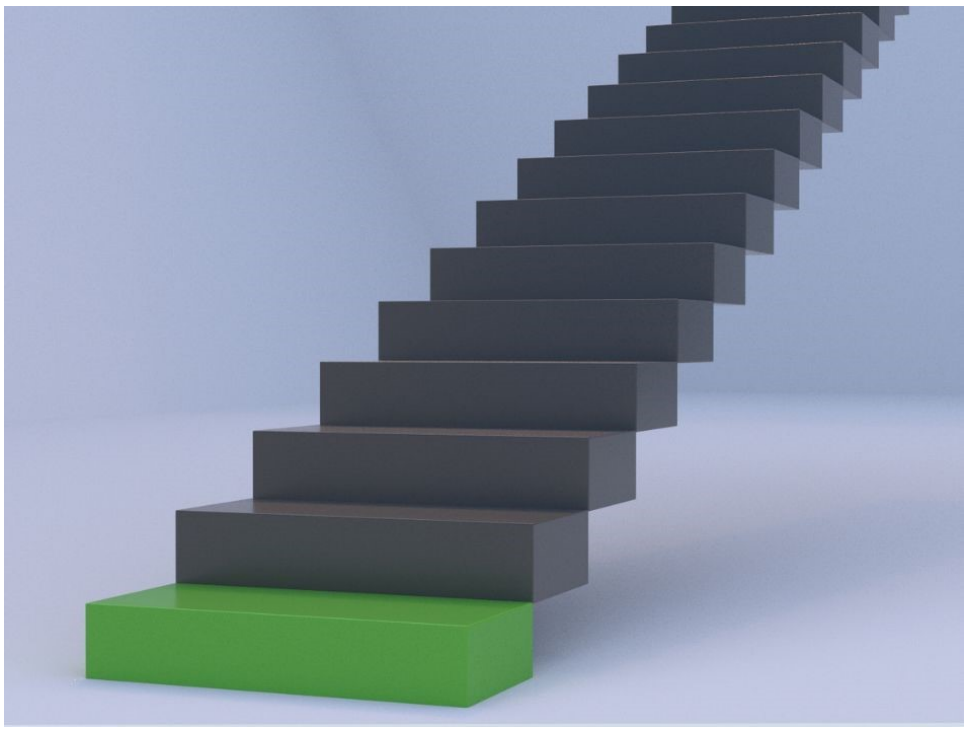
🏷️ Indications

Teclistamab is a **bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager** indicated for adult patients:

- **Relapsed or refractory multiple myeloma** who have received **at least 4 prior lines of therapy**, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

Note: This indication is approved under accelerated approval based on response rate and durability of response. Continued approval may be contingent upon verification of clinical benefit in confirmatory trials.

💊 Dosing and Administration



Teclistamab is administered **subcutaneously (SQ)** initially as part of a **weekly (every 7 day)** dosing cycle.

For individuals who **achieve and maintain a complete response** following a **minimum of 6-month treatment** with teclistamab, patients **will continue therapy as part of a biweekly (every 14 day)** dosing cycle.

Teclistamab has a unique **step-up dosing** schedule as shown below to reduce the risk and severity of cytokine release syndrome (CRS).

Teclistamab Weekly Dosing Schedule			
Dosing Schedule		**Day**	**Dose[c,d] / Route**
Step-up Dosing Schedule	**Step-up Dose 1**	Day 1	0.06 mg/kg SQ
	Step-up Dose 2	Day 4[a]	0.3 mg/kg SQ
	Treatment Dose	Day 7[b]	1.5 mg/kg SQ
Weekly Dosing Schedule		One week following first treatment dose (Cycle 1 Day 7) and weekly thereafter	1.5 mg/kg once weekly SQ

[a]Step-up dose 2 may be given between 2 to 4 days after step-up dose 1 and may be given up to 7 days after step-up dose 1 to allow for resolution of adverse reactions.

[b]First treatment dose may be given between 2 to 4 days after step-up dose 2 and may be given up to 7 days after step-up dose 2 to allow for resolution of adverse reactions.

[c]Administer pre-medications prior to teclistamab dose and monitor accordingly
- dexamethasone 16 mg (IV/PO) or equivalent;
- diphenhydramine 50 mg (IV/PO) or equivalent;
- acetaminophen 650 mg to 1000 mg (IV/PO) or equivalent

[d]Patients should be hospitalized for 48 hours following administration of all step-up doses

Teclistamab Dosing Schedule (Biweekly) for Patients Who Have Achieved and Maintained a Complete Response or Better for a Minimum of 6 Months		
Dosing Schedule	**Day**	**Dose/Route**
Biweekly Dosing Schedule	Day 1 every 14 days (2 weeks)	1.5 mg/kg SQ

Recommendations for Restarting Teclistamab after Dose Delay		
Last Dose Administered	**Time from Last Dose Administered**	**Teclistamab Recommendation**
Step-up Dose 1	> 7 days	Restart step-up dosing schedule at step-up dose 1 (0.06 mg/kg).[a]
Step-up Dose 2	8 to 28 days	Repeat step-up dose 2 (0.3 mg/kg)[a] and continue step-up dosing schedule as planned.
	> 28 days[b]	Restart step-up dosing schedule at step-up dose 1 (0.06 mg/kg).[a]
Any weekly treatment dose	≤ 28 days	Continue teclistamab at last treatment dose in weekly schedule (1.5 mg/kg once weekly).
	29 to 56 days[b]	Restart step-up dosing schedule at step-up dose 2 (0.3 mg/kg).[a]
	> 56 days[b]	Restart step-up dosing schedule at step-up dose 1 (0.06 mg/kg).[a]
Any biweekly (every 2 weeks) treatment dose	≤ 63 days[b]	Continue teclistamab at last treatment dose in biweekly schedule (1.5 mg/kg once biweekly).
	64 to 112 days[b]	Restart step-up dosing schedule at step-up dose 2 (0.3 mg/kg).[a]
	> 112 days[b]	Restart step-up dosing schedule at step-up dose 1 (0.06 mg/kg).[a]

[a]Administer pre-medications prior to teclistamab dose and monitor accordingly
- dexamethasone 16 mg (IV/PO) or equivalent;
- diphenhydramine 50 mg (IV/PO) or equivalent;
- acetaminophen 650 mg to 1000 mg (IV/PO) or equivalent

[b]Consider benefit-risk of restarting teclistamab in patients who require a dose delay of more than 28 days due to an adverse reaction

Prophylaxis

Prior to starting treatment with teclistamab, **consider the initiation of antiviral prophylaxis** to prevent herpes zoster reactivation per guidelines.

⚠️ CRS

What is it? Cytokine release syndrome (CRS) is a systemic inflammatory response that can occur when the immune system is activated and releases large amounts of cytokines—proteins that help regulate immune responses.

- **Signs and symptoms:** pyrexia, hypotension, hypoxia, dyspnea, chills, and tachycardia.
- CRS is frequently graded using the American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria.

Why it matters. CRS occurred in **72% of patients** who received teclistamab at the recommended dosage, in the clinical trial, MajesTEC-1.

- **Most CRS events** were **reported in the step-up dosing schedule**, either at step-up dose 1 (42%), step-up dose 2 (35%), or the initial treatment dose (24%) and were primarily Grade 1 (50%).
    - **CRS did reoccur** in approximately **33%** patients regardless of their dosing schedule.
- The **median time to onset** of CRS across all doses was **2 days** (range: 1 to 6) post-administration. The **median duration of CRS** was **2 days** (range: 1 to 9).
- Care teams should monitor for signs/symptoms of CRS and **withhold or permanently discontinue teclistamab based on severity**.

The bottom line. While CRS was primarily low grade, predictable, and manageable.

🧠 Neurotoxicity (including ICANS)

What is it? Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) is characterized by various neurological symptoms resulting from the activation of the immune system and the resultant inflammatory processes.

- **Signs and symptoms:** encephalopathy, headaches, seizures, aphasia, motor deficits, ataxia, and tremor.
- ICANS is frequently graded using the ASTCT consensus criteria.

Why it matters. Neurological toxicity, including ICANS, occurred in **57% of patients** in MajesTEC-1, and **Grade 3 or 4 neurological toxicity** was reported in **2.4%** of patients. The most common neurological toxicities included: headache, sensory neuropathy, encephalopathy, and motor dysfunction.

- With a longer follow-up period, two patients (one each) who received teclistamab experienced:
    - Grade 4 seizure
    - Fatal Guillain-Barré Syndrome
- **ICANS** specifically, was reported in **6%** of patients and reoccurred in **1.8% of patients**.
    - **Most ICANS** events were reported in the **step-up dosing schedule**, either at step-up dose 1 (1.2%) or step-up dose 2 (0.6%). Following the introduction of the treatment dose as part of the weekly dosing schedule, 1.8% patients reported ICANS.
        - ICANS symptoms were primarily reported with confusion and dysgraphia.

    - The **median time to onset** of ICANS across all doses was **4 days** (range: 2 to 8) post-administration. The **median duration of ICANS** was **3 days** (range: 1 to 20). The onset of ICANS may be experienced concurrently with CRS, in the absence of CRS, or even following the resolution of CRS.
- Care teams should monitor for signs/symptoms of ICANS and **discourage patients from driving or operating heavy machinery** that may be considered potentially dangerous **during the step-up dosing schedule and 48 hours following completion of the step-up schedule** the in event of any new onset of neurological toxicity occurs or until symptoms resolve.
    - Additionally, care teams should **consider withholding or permanently discontinuing teclistamab based on severity.**

The bottom line. ICANS events were less common compared to CRS but resolved relatively quickly over a few days.

🚨 Other Toxicities

Teclistamab may cause other adverse reactions including **hypersensitivity reactions, infection, neutropenia and other toxicities such as hepato- and embryo-fetal toxicity.**

Why it matters. In addition to the risks of CRS and neurotoxicity (including ICANS), care teams need to be on the lookout for other **teclistamab**-associated toxicities.

Infections. Teclistamab may cause serious and fatal infections.

- **Serious infections**, including opportunistic infections, occurred in **30% of patients**, with **Grade 3 or 4 infections** in **35%**, and **fatal** infections in **4.2%**.

The bottom line. Care teams should **monitor patients for signs of infection before and during treatment** and **consider withholding or permanent discontinuation based on the severity**.

- Additionally, care teams should **administer prophylactic antimicrobials according to the local guidelines** and monitor immunoglobulin levels during treatment.

Neutropenia. Teclistamab may cause neutropenia and febrile neutropenia.

- In the clinical trial, **decreased neutrophils** occurred in **84%** of patients, with **Grade 3 or 4 decreased neutrophils in 56%**.
    - **Febrile neutropenia** occurred in **3%** of patients.

The bottom line. Care teams should monitor complete blood counts throughout treatment.

- **Withhold or discontinue teclistamab based on neutropenia severity**.

Hepatotoxicity. Teclistamab may cause hepatotoxicity. In MajesTEC-1 elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and bilirubin were reported as followed:

- **ALT:** 28% (Grade 3 or 4: 1.8%)
- **AST:** 34% (Grade 3 or 4: 1.2%)
- **Bilirubin:** 6% (Grade 3 or 4: 0.6%)

The bottom line. Care teams should **monitor liver enzymes and bilirubin throughout treatment** as clinically indicated and **consider withholding or permanent discontinuation of teclistamab based on the severity**.

Hypersensitivity and Other Administration Reactions. Teclistamab may cause both local injection-site reactions and systemic administration-related reactions.

- In the clinical trial, **1.2% of patients** experienced a **systemic reaction** which included both Grade 1 recurrent pyrexia and swollen tongue.
- Additionally, **35%** of patients in clinical trial experienced **local reactions**, which included Grade 1 or 2 injection site reactions, 30% and 4.8%, respectively.

The bottom line. Care teams should **monitor patients for hypersensitivity and infusion-related reactions throughout treatmen**t as clinically indicated.

- Additionally, care teams should **consider withholding or permanent discontinuation of teclistamab based on the severity**.

Embryo-Fetal Toxicity. Teclistamab may cause fetal harm when administered to a pregnant woman.

- Advise **females of reproductive potential** to use effective contraception **during treatment and for 5 months** after the last dose.
- Verify pregnancy status before initiating teclistamab.

Use in Specific Populations.

- **Lactation:** Advise women not to breastfeed during treatment and for 5 months after the last dose.
- **Geriatric Use:** No overall differences were observed in patients between 65 to 74 years of age compared to younger patients. At this time, there is an insufficient number of patients aged 75 years or older to assess whether there are differences in safety and efficacy.
- **Pediatric Use:** At this time, no safety and effectiveness data has been established in pediatric patients.

Teclistamab has a **Risk Evaluation and Mitigation Strategy (REMS)** to mitigate the risk of CRS and neurologic toxicity, including ICANS.

Why it matters. Prescribers, pharmacies, and healthcare settings have specific requirements per the TECVAYLI and TALVEY REMS to treat patients with teclistamab.

Notable requirements of the TECVAYLI and TALVEY REMS include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- Prescribers must counsel patients receiving teclistamab about the risk of CRS and neurologic toxicity, including ICANS, and provide patients with Patient Wallet Card.
- Pharmacies and healthcare settings that dispense teclistamab must be certified with the TECVAYLI and TALVEY REMS program and must verify prescribers are certified through the TECVAYLI and TALVEY REMS program.
- Wholesalers and distributers must only distribute TECVAYLI to certified pharmacies or healthcare settings.

Steps for a prescriber to become certified:

1. Review the prescribing training program and adverse reaction management slides.
2. Successfully complete the knowledge assessment and submit it to the REMS
3. Complete the prescriber enrollment form and submit it to the REMS
4. Before treatment initiation (first step-up dose), counsel patients and/or their caregivers using the patient wallet card. Counsel patients that they should be hospitalized and

monitored for signs and symptoms of CRS and neurologic toxicity, including ICANS, for 48 hours after administration of all doses within the step-up dosing schedule.

Steps for pharmacies and healthcare settings to become certified:

1. Designate an Authorized Representative (AR) for the pharmacy and healthcare setting
    a. The AR at the pharmacy can be a pharmacist, pharmacy technician, or any responsible individual assigned by the pharmacy.
    b. The AR at the healthcare setting can be a pharmacist, nurse, or any responsible individual assigned by the healthcare setting.
    c. Note: One delegate may be added to support the AR at each setting.
2. AR must review the Pharmacy and Healthcare Setting Training Program slides.
3. AR must complete the Pharmacy and Healthcare Setting Enrollment Form and submit it to the REMS
4. Train all relevant staff involved in dispensing teclistamab on the REMS requirements using the Pharmacy and Healthcare Setting Training Program slides.
    a. Before dispensing, obtain authorization to dispense each prescription by contacting the REMS to verify the prescriber is certified.

Go deeper. For more information on the TECVAYLI and TALVEY REMS program, click here.

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References:

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3. Usmani SZ, Garfall AL, van de Donk NWCJ, et al. Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study. *Lancet*. 2021;398(10301):665-674. doi:10.1016/S0140-6736(21)01338-6.
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