Summary Report of Benefit-Risk Assessment

TECVAYLI SOLUTION FOR INJECTION 10MG/ML
TECVAYLI SOLUTION FOR INJECTION 90MG/ML

NEW DRUG APPLICATION

Active Ingredient(s)	Teclistamab
Product Registrant	Johnson & Johnson International (Singapore) Pte Ltd
Product Registration Number	SIN16948P, SIN16949P
Application Route	Abridged evaluation
Date of Approval	16 February 2024

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A INTRODUCTION

Tecvayli is indicated as monotherapy for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, and have demonstrated disease progression on the last therapy.

The active substance, teclistamab, is a bispecific antibody that targets the CD3 receptor expressed on the surface of T cells and B-cell maturation antigen (BCMA), which is expressed on the surface of malignant multiple myeloma B-lineage cells, late-stage B cells and plasma cells. Teclistamab, with its dual binding sites, draws $CD3^+$ T cells in close proximity to $BCMA^+$ cells, resulting in T cell activation and T cell-mediated cytotoxicity against BCMA-expressing myeloma cells.

Tecvayli is available as solution for injection containing 30mg/3ml or 153mg/1.7ml of Teclistamab. Other ingredients in the vial are EDTA disodium salt dihydrate, glacial acetic acid, polysorbate 20, sodium acetate trihydrate, sucrose and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, Teclistamab, is manufactured at Janssen Sciences Ireland UC, Cork, Ireland. The drug product, Tecvayli Solution for Injection 30mg/3ml & Tecvayli Solution for Injection 153ml/1.7ml, is manufactured at Patheon Manufacturing Services LLC, North Carolina, United States.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities were appropriately performed. Potential and actual impurities are adequately controlled in the specifications.

The drug substance specifications were established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The packaging is single use 1L polycarbonate bioprocess container with a polypropylene screw closure. The stability data presented was adequate to support the storage of the drug substance at -40 ±10°C with a shelf-life of 18 months.

Drug product:

The manufacturing process involves pooling and homogenisation of the formulated drug substance, followed by prefiltration, sterile filtration and aseptic filling. This is considered a standard manufacturing process.

The manufacturing site is compliant with GMP. Proper development and validation studies were conducted with 3 consecutive batches. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications were established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The container closure system is Type I glass vial with rubber stopper and aluminium seal with flip-off cap containing 3ml (for 10mg/ml) or 1.7ml (for 90mg/ml) product. The stability data submitted was adequate to support the approved shelf-life of 18 months when stored at 2 to 8ºC. The in-use period after opening is to store at 2ºC to 8ºC or ambient temperature (15ºC to 30ºC) for not more than 20 hours and was supported by in-use stability data.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of teclistamab in the treatment of RRMM was based primarily on one pivotal study, MajesTEC-1. This was a first-in-human, Phase 1/2, open-label, multicentre, dose escalation study to evaluate the safety, tolerability, pharmacokinetics, and anti-myeloma activity of teclistamab in patients with RRMM who had received at least three prior therapies and were exposed to a proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and an anti-CD38 monoclonal antibody.

The Phase 1 portion consisted of the dose escalation (Part 1) and dose expansion (Part 2) phases to assess the safety, tolerability, and the recommended Phase 2 doses (RP2Ds). In Part 1, subjects received teclistamab via intravenous (IV) injection at doses of 0.0003 to 0.0192 mg/kg every 2 weeks (Q2W) and 0.0192 to 0.72 mg/kg weekly, or via subcutaneous (SC) injection at doses of 0.08 to 1.5 mg/kg weekly. In Part 2, subjects received teclistamab IV at 0.72 mg/kg weekly or teclistamab SC at 1.5 mg/kg weekly. Based on the pharmacokinetic (PK), pharmacodynamic, safety, and efficacy data obtained from Phase 1, the RP2D was determined to be 1.5 mg/kg SC weekly preceded by two step-up doses of 0.06 mg/kg and 0.3 mg/kg.

The Phase 2 portion was the dose expansion phase consisting of two cohorts (Cohort A and Cohort C). Cohort A enrolled subjects who had received at least 3 prior therapies and were exposed to a PI, an IMiD and an anti-CD38 monoclonal antibody. Cohort C enrolled subjects who had received an anti-BCMA therapy (antibody drug conjugate [ADC] or chimeric antigen receptor T cell [CAR-T]) in addition to the therapeutic classes and lines of therapy required for Cohort A.

The primary efficacy data were assessed based on the pivotal RP2D population, including subjects from the Phase 1 and Phase 2 (Cohort A) study who were treated at the RP2D dose (i.e., 1.5 mg/kg SC weekly). Cohort C of Phase 2 was not included in the primary efficacy analysis.

In the pivotal RP2D population, subjects received step-up doses of 0.06 mg/kg and 0.3 mg/kg followed by the treatment dose of 1.5 mg/kg once weekly; all doses were administered subcutaneously. A control arm was not included in the study, and this was considered acceptable as there was no standard treatment in heavily treated RRMM patients. All subjects were required to receive the following pretreatment medications prior to each step-up dose and the first treatment dose: steroids (dexamethasone 16 mg), antihistamines (diphenhydramine 50 mg or equivalent), and antipyretics (acetaminophen 650 mg to 1000 mg or equivalent). Additionally, subjects who experienced Grade ≥2 cytokine release syndrome (CRS) or systemic administration-related reactions (sARRs) were required to receive dexamethasone prior to the next dose of teclistamab, and subjects who experienced any grade CRS or sARRs were required to receive antihistamine and antipyretic prior to at least the next dose of teclistamab. Subjects were treated until disease progression, unacceptable toxicity, withdrawal of consent, death, or end of study (defined as 2 years after the last subject's first dose).

The primary efficacy endpoint was overall response rate (ORR), defined as the proportion of subjects who achieved partial response (PR) or better response (PR, very good partial response [VGPR], complete response [CR], or stringent complete response [sCR]), during or after study treatment but before the start of subsequent anti-myeloma therapy. Responses were assessed by the Independent Review Committee (IRC) using the International Myeloma Working Group (IMWG) 2016 response criteria. Key secondary efficacy endpoints included duration of response (DOR), VGPR or better rate, CR or better rate, sCR rate, time to response (TTR), progression-free survival (PFS), overall survival (OS), minimal residual disease (MRD)-negativity rate, and ORR in subjects with high-risk cytogenetics at baseline.

The efficacy population comprised 150 subjects who received the pivotal RP2D: 40 subjects in Phase 1 and 110 subjects in Cohort A in Phase 2. The median age was 64.5 years (range: 33 to 84 years), of which 23 subjects (15.3%) were 75 years of age and above. The majority of the subjects were male (88 [58.7%]) and White (134 [89.3%]). Fifty-three subjects (35.3%) had an Eastern Cooperative Oncology Group (ECOG) score of 0 and 97 subjects (64.7%) had an ECOG score of 1. IgG was the most common immunoglobulin isotype, presenting in 81 subjects (54.0%) treated at the pivotal RP2D. The median time from diagnosis of multiple myeloma to enrolment was 6.1 years (range: 0.8 to 22.7 years). Twenty-seven subjects (18%) had 1 or more extramedullary plasmacytomas at baseline. Of the 133 subjects with baseline cytogenetic data reported, 36 (27.1%) had at least 1 high-risk abnormality, most frequently del(17p). Most subjects were International Staging System (ISS) Stage I at baseline (79 subjects [53.4%]), and 17 subjects (11.5%) were ISS Stage III at baseline.

In total, 145 of the 150 subjects received at least 3 prior lines of multiple myeloma therapy. The median number of prior lines of therapy was 5 (range: 2 to 14). All 150 subjects (100.0%) had received prior therapy with a PI, an IMiD, and an anti-CD38 monoclonal antibody, and 116 subjects (77.3%) were triple-class refractory (refractory to a PI, an IMiD, and an anti-CD38 monoclonal antibody).

Summary of key efficacy results

	Teclistamab RP2D (N=150)
Primary endpoint	
ORR per BICR, % (95% CI)	62.7 (54.4, 70.4)
Key secondary endpoints	
VGPR or better, % (95% CI)	58.7 (50.3, 66.6)
CR or better, % (95% CI)	32.0 (24.6, 40.1)

sCR, % (95% CI)	25.3 (18.6, 33.1)
Median DOR (months) (95% CI)	NE (11.5, NE)
Median PFS (months) (95% CI)	10.1 (8.0, NE)
Median OS (months) (95% CI)	18.3 (18.3, NE)

NE=not estimable

At the proposed dose of 1.5 mg/kg once weekly following 2 step-up doses with a median follow-up of 9.9 months, the ORR in the RP2D population was 62.7% (95% CI: 54.4%, 70.4%) as assessed by the IRC based on IMWG 2016 criteria. The majority (79.8%) of the responders maintained their responses until the clinical data cutoff date of 09 Nov 2021. The ORR results were consistent in various sensitivity analyses as well as in pre-defined subgroups. In the subgroup analysis stratified by prior lines of therapy, while the majority of patients had received ≥ 4 prior lines of therapy (76.0%), patients who received < 4 prior lines of therapy (24.0%) showed an ORR of 75.0% which was comparable to the overall population (ORR of 62.7%). The magnitude of the ORR was substantial compared with current approved treatments for heavily treated RRMM patients (ranged from 25% to 32%).

The efficacy results were further supported by secondary efficacy endpoints. The median DOR was not reached at the clinical data cutoff date. The probability of responders remaining in response at 12 months was 67.2% (95% CI: 49.4%, 79.9%). The response rates for VGPR or better, CR or better, and sCR were 58.7% (95% CI: 50.3%, 66.6%), 32.0% (95% CI: 24.6%, 40.1%), and 25.3% (95% CI: 18.6%, 33.1%), respectively. The median PFS by IRC assessment was 10.1 months (95% CI: 8.0, NE) the median OS was 18.3 months (95% CI: 18.3, NE). The data was not mature at the data cutoff date. There were limitations with the early phase, single-arm study, which did not allow meaningful interpretation of the time-to-event endpoints in respect of PFS and OS.

Nevertheless, considering the limited treatment options for heavily treated RRMM patients, and that ORR demonstrated with teclistamab compared favourably with current available treatments for heavily treated RRMM patients, the available data provided reasonable evidence to support the efficacy of teclistamab as monotherapy for the treatment of adult patients with RRMM who have received at least three prior therapies, including a PI, an IMiD, and an anti-CD38 monoclonal antibody, and have demonstrated disease progression on the last therapy.

A Phase 3, open-label, randomised, multicenter study (Study MajesTEC-3) comparing teclistamab in combination with daratumumab (tec-dara) versus daratumumab, pomalidomide, and dexamethasone (dpd) or daratumumab, bortezomib, and dexamethasone (dvd) in RRMM patients who have previously received 1 to 3 prior line(s) of therapy, including a PI and lenalidomide, is ongoing. The approval for teclistamab is subject to the condition attached to the product registration for the company to submit the final study report of this study to confirm the efficacy and safety of teclistamab in the treatment of patients with RRMM.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of teclistamab was primarily based on safety data derived from the pivotal Phase 1/2 study Majes TEC-1, comprising a total of 165 patients who received at least one dose of teclistamab at the proposed dosing regimen (pivotal RP2D). The safety assessment was further supported by safety data from the overall study population comprising 340 patients. At the time of data cutoff date (09 Sep 2021), the median duration of follow-up was 9.7 months for the overall study population and 7.2 months for the pivotal RP2D population.

Overview of safety profile

AE	Teclistamab RP2D (N=165)
Any AE	165 (100.0%)
Treatment-related AE	152 (92.1%)
SAE	88 (53.3%)
Treatment-related SAE	33 (20.0%)
Discontinuations due to AE	1 (0.6%)
Deaths due to AE	9 (5.5%)
Deaths due to AE (≤30 days after last dose)	6 (3.6%)

All subjects in the pivotal RP2D population experienced at least 1 treatment-emergent adverse event (TEAE), and 92.1% experienced at least 1 Grade 3 or Grade 4 TEAE. The most frequently reported TEAEs (≥20% subjects) were CRS (71.5%), neutropenia (65.5%), anaemia (49.7%), thrombocytopenia (38.2%), lymphopenia (33.9%), injection site erythema (25.5%), fatigue (24.8%), nausea (24.2%), headache (21.8%) and diarrhoea (20.6%). The most frequently reported (≥10% of subjects) Grade 3 or 4 TEAEs were neutropenia (57.0%), anaemia (34.5%), lymphopenia (32.1%) and thrombocytopenia (21.2%).

Serious TEAEs were reported for 88 subjects (53.3%). Treatment discontinuation due to TEAEs were infrequently reported (0.6%). Among the subjects who received pivotal RP2D, 24.2% reported deaths as of the data cutoff date, of which the majority (18.2%) were due to disease progression.

The AEs of special interest (AESIs) with teclistamab included CRS (71.5%), neurologic toxicities (51.5%), injection-site reactions (35.2%), hypogammaglobulinemia (72.1%), cytopenias (89.1%), and infections (63.0%). CRS was reported in 118 subjects (71.5%), among which 54 (32.7%) experienced recurrent CRS events. All CRS events were Grade 1 or 2, except 1 subject who experienced Grade 3 CRS. No death or discontinuation due to CRS was reported. Neurologic AEs were reported for 85 subjects (51.5%) treated at pivotal RP2D. Immune effector cell-associated neurotoxicity syndrome (ICANS) events were reported for 5 subjects (3.0%) and all were Grade 1 or 2 and resolved at the time of clinical cutoff date. There was no death or discontinuation due to ICANS reported in the study. The safety information and recommendations on the management of the AEs have been adequately described in the local package insert.

Overall, the safety profile of teclistamab was manageable and considered acceptable for heavily treated RRMM patients who have limited treatment options.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Multiple myeloma is a rare disease characterised by the proliferation of neoplastic clones of plasma cells derived from B lymphocytes. Despite multiple therapeutic options, the disease remains incurable and often recurs. Patients who are heavily treated have poor outcomes and limited treatment options. Hence, there is an unmet medical need for more therapeutic options in heavily treated RRMM patients.

The clinical efficacy of teclistamab was evaluated in a Phase 1/2, open-label, single-arm study (MajesTEC-1) conducted in patients with RRMM who had received at least three prior therapies and were exposed to a PI, an IMiD, and an anti-CD38 monoclonal antibody. The

ORR as assessed by the IRC was 62.7% (95% CI: 54.4% to 70.4%) with a median follow-up of 9.9 months. The median DOR was not reached with the probability of responders remaining in response at 12 months at 67.2% (95% CI: 49.4% to 79.9%). The magnitude of efficacy was substantial compared with current available treatments for heavily treated RRMM patients. The efficacy results were further supported by subgroup analyses of ORR and key secondary efficacy endpoints. The time-to-event endpoints (i.e., PFS and OS) were reported but could not be meaningfully interpreted due to lack of a control arm.

The safety profile of teclistamab was consistent with its mechanism of action and was manageable. The AESIs reported with teclistamab included CRS, neurologic toxicities, injection-site reactions, hypogammaglobulinemia, cytopenias and infections. These risks have been adequately described in the local package with appropriate warnings and precautions, as well as dose adjustment recommendations in the event of toxicities.

In view of the limited treatment options for heavily treated RRMM patients, the risks associated with teclistamab therapy are considered acceptable, hence the benefits of teclistamab outweigh the risks in the treatment of RRMM patients who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, and have demonstrated disease progression on the last therapy.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Tecvayli as monotherapy for the treatment of adult patients with RRMM who have received at least three prior therapies, including proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, and have demonstrated disease progression on the last therapy, was deemed favourable and approval of the product registration was granted on 16 February 2024. The approval of this application is subject to conditions for submission of the final study reports of the Phase 1/2 study (Study MajesTEC-1) and the Phase 3 study (Study MajesTEC-3).

APPROVED PACKAGE INSERT AT REGISTRATION

PRODUCT NAME

TECVAYLI® (teclistamab) solution for injection

DOSAGE FORMS AND STRENGTHS

TECVAYLI® (teclistamab) is a humanized immunoglobulin G4-proline, alanine, alanine (IgG4-PAA) bispecific antibody targeting the B cell maturation antigen (BCMA) and CD3 receptors, produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology.

TECVAYLI® is a colorless to light yellow, with a pH of 5.2 and osmolarity of approximately 296 mOsm/L (10 mg/mL solution for injection), and approximately 357 mOsm/L (90mg/mL solution for injection), preservative-free solution for injection.

TECVAYLI® is available in the following presentations:

- Each 3 mL vial contains 30 mg of teclistamab (10 mg of teclistamab per mL)
- Each 1.7 mL vial contains 153 mg of teclistamab (90 mg of teclistamab per mL)

For excipients, see *List of Excipients*.

CLINICAL INFORMATION

Indications

TECVAYLI® as monotherapy is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, and have demonstrated disease progression on the last therapy.

Dosage and Administration

Dosage – Adults

TECVAYLI® should be administered by subcutaneous injection only.

Administer pretreatment medications prior to each dose of the TECVAYLI® step-up dosing schedule (see *Dosage and Administration – Pretreatment medications*).

Recommended dosing schedule

The recommended dosing schedule for TECVAYLI® is provided in Table 1. The recommended dosage of TECVAYLI® is step-up doses of 0.06 mg/kg and 0.3 mg/kg followed by 1.5 mg/kg once weekly until disease progression or unacceptable toxicity.

Administer TECVAYLI® according to the step-up dosing schedule in Table 1 to reduce the incidence and severity of cytokine release syndrome (CRS). Due to the risk of cytokine release syndrome (CRS), instruct patients to remain within proximity of a healthcare facility and monitor

patients for signs and symptoms daily for 48 hours after administration of all doses within the TECVAYLI® step-up dosing schedule (see *Dosage and Administration – Administration* and *Warnings and Precautions - Cytokine Release Syndrome*).

Failure to follow the recommended doses or dosing schedule for initiation of therapy or re-initiation of therapy after dose delays may result in increased frequency and severity of adverse events related to mechanism of action, particularly cytokine release syndrome (see *Dosage and Administration - Dosage modifications* and *Warnings and Precautions – Cytokine Release Syndrome*).

Table 1: TECVAYLI® dosing schedule

Dosing schedule	Day	Dose[a]	
Step-up dosing schedule[b]	Day 1	Step-up dose 1	0.06 mg/kg single dose
	Day 3[c]	Step-up dose 2	0.3 mg/kg single dose
	Day 5[d]	First treatment dose	1.5 mg/kg single dose
Weekly dosing schedule[b]	One week after first treatment dose and weekly thereafter[e]	Subsequent treatment doses	1.5 mg/kg once weekly

[a] Dose is based on actual body weight and should be administered subcutaneously.

[b] See Table 2 for recommendations on restarting TECVAYLI® after dose delays.

[c] Step-up dose 2 may be given between 2 to 7 days after Step-up dose 1.

[d] First treatment dose may be given between 2 to 7 days after Step-up dose 2. This is the first full treatment dose (1.5 mg/kg).

[e] Maintain a minimum of five days between weekly treatment doses.

For guidance regarding restarting therapy with TECVAYLI® after dose delays, (see *Dosage and Administration - Restarting TECVAYLI® after dose delays*).

Pretreatment medications

Administer the following pretreatment medications 1 to 3 hours before each dose of the TECVAYLI® step-up dosing schedule to reduce the risk of cytokine release syndrome (see *Warnings and Precautions - Cytokine Release Syndrome* and *Adverse Reactions*).

- Corticosteroid (oral or intravenous dexamethasone, 16 mg)
- Antihistamine (oral or intravenous diphenhydramine, 50 mg or equivalent)
- Antipyretics (oral or intravenous acetaminophen, 650 mg to 1000 mg or equivalent)

Administration of pretreatment medications may be required prior to administration of subsequent doses of TECVAYLI® in the following patients: (see *Dosage and Administration – Dosage modifications*).

- Patients who repeat doses within the TECVAYLI® step-up dosing schedule following a dose delay (see *Dosage and Administration – Restarting TECVAYLI® after dose delays*).
- Patients who experienced CRS following the prior dose of TECVAYLI® (see *Dosage and Administration – Dosage modifications*).

Prophylaxis for herpes zoster virus reactivation

Prior to starting treatment with TECVAYLI®, anti-viral prophylaxis should be considered for the prevention of herpes zoster virus reactivation per local institutional guidelines.

Restarting TECVAYLI® after dose delays

If a dose of TECVAYLI® is delayed, restart therapy based on the recommendations listed in Table 2 and resume the treatment schedule accordingly (see *Dosage and Administration-Dosage – Adults*). Administer pretreatment medications as indicated in Table 2 and monitor patients following administration of TECVAYLI® accordingly (see *Dosage and Administration – Pretreatment medications* and *Dosage and Administration - Administration*).

Table 2: Recommendations for Restarting TECVAYLI® after Dose Delay

Last Dose Administered	Duration of Delay from the Last Dose Administered	Action
Step-up Dose 1	7 days or less	Resume TECVAYLI® step-up dosing schedule at Step-up Dose 2 (0.3 mg/kg).[a]
	More than 7 days	Restart TECVAYLI® step-up dosing schedule at Step-up Dose 1 (0.06 mg/kg).[a]
Step-up Dose 2	7 days or less	Resume TECVAYLI® step-up dosing schedule at Treatment Dose (1.5 mg/kg). [a]
	8 days to 28 days	Resume TECVAYLI® step-up dosing schedule at Step-up Dose 2 (0.3 mg/kg). [a]
	More than 28 days	Restart TECVAYLI® step-up dosing schedule at Step-up Dose 1 (0.06 mg/kg). [a]
Any Treatment Dose	28 days or less	Resume TECVAYLI® at Treatment Dose (1.5 mg/kg) once weekly.
	More than 28 days	Restart TECVAYLI® step-up dosing schedule at Step-up Dose 1 (0.06 mg/kg). [a]

[a] Administered pretreatment medications prior to TECVAYLI® dose and monitor accordingly. (see *Dosage and Administration – Pretreatment medications* and *Dosage and Administration - Administration*).

Dosage modifications

Do not skip step-up doses of TECVAYLI®.

Dose reductions of TECVAYLI® are not recommended.

Dose delays may be required to manage toxicities related to TECVAYLI® (see *Warnings and Precautions*).

See Table 3 for recommended actions for adverse reactions following administration of TECVAYLI®.

Table 3: Recommended Actions for Adverse Reactions Following Administration of TECVAYLI®

Adverse Reactions	Grade	Actions
Cytokine Release Syndrome (CRS)[a] (see *Warnings and Precautions*)	Grade 1	• Withhold TECVAYLI® until adverse reaction resolves. • See Table 4 for management of cytokine release syndrome. • Administer pretreatment medication prior to next dose of TECVAYLI®.
	Grade 2 Grade 3 (Duration: less than 48 hours)	• Withhold TECVAYLI® until adverse reaction resolves. • See Table 4 for management of cytokine release syndrome. • Administer pretreatment medications prior to next dose of TECVAYLI®. • Monitor patient daily for 48 hours following the next dose of TECVAYLI®. Instruct patients to remain within proximity of a healthcare facility during daily monitoring.
	Grade 3 (Recurrent or duration: more than 48 hours) Grade 4	• Permanently discontinue therapy with TECVAYLI®. • See Table 4 for management of cytokine release syndrome.
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) (see *Warnings and Precautions*)	Grade 1	• Withhold TECVAYLI® until adverse reaction resolves. • See Table 5 for management of immune effector cell-associated neurotoxicity syndrome.
	Grade 2 Grade 3 (First occurrence)	• Withhold TECVAYLI® until adverse reaction resolves. • See Table 5 for management of immune effector cell-associated neurotoxicity syndrome. • Monitor patient daily for 48 hours following the next dose of TECVAYLI®. Instruct patients to remain within proximity of a healthcare facility during daily monitoring.
	Grade 3 (Recurrent) Grade 4	• Permanently discontinue therapy with TECVAYLI®. • See Table 5 for management of immune effector cell-associated neurotoxicity syndrome.
Infections (see *Warnings and Precautions*)	All Grades	• Do not administer TECVAYLI® step-up dosing schedule in patients with active infection.
	Grade 3 Grade 4	• Withhold subsequent treatment doses of TECVAYLI® until infection improves to Grade 2 or better.
	Absolute neutrophil count less than 0.5×10^9/L	• Withhold TECVAYLI® until absolute neutrophil count is 0.5×10^9/L or higher.

Hematologic Toxicities (see *Warnings and Precautions* and *Adverse Reactions*)	Febrile neutropenia	• Withhold TECVAYLI® until absolute neutrophil count is 1.0×10^9/L or higher and fever resolves.
	Hemoglobin less than 8 g/dL	• Withhold TECVAYLI® until hemoglobin is 8 g/dL or higher.
	Platelet count less than 25000/µL Platelet count between 25000/µL and 50000/µL with bleeding	• Withhold TECVAYLI® until platelet count is 25000/µL or higher and no evidence of bleeding.
Other Adverse Reactions (see *Adverse Reactions*)	Grade 3 Grade 4	• Withhold TECVAYLI® until adverse reaction improves to Grade 2 or better.

[a] Based on American Society for Transplantation and Cellular Therapy (ASTCT) grading.

Management of severe adverse reactions

Cytokine release syndrome (CRS)

Identify CRS based on clinical presentation (see *Warnings and Precautions - Cytokine Release Syndrome*). Evaluate and treat other causes of fever, hypoxia, and hypotension.

If CRS is suspected, withhold TECVAYLI® until the adverse reaction resolves (see Table 3) and manage according to the recommendations in Table 4. Administer supportive care for CRS (including but not limited to anti-pyretic agents, intravenous fluid support, vasopressors, supplemental oxygen, etc.) as appropriate. Consider laboratory testing to monitor for disseminated intravascular coagulation (DIC), hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function.

Table 4: Recommendations for Management of Cytokine Release Syndrome with Tocilizumab and Corticosteroids

Grade[e]	Presenting Symptoms	Tocilizumab[a]	Corticosteroids[b]
Grade 1	Temperature ≥100.4°F (38°C)[c]	May be considered.	Not applicable
Grade 2	Temperature ≥100.4°F (38°C)[c] with either: Hypotension responsive to fluids and not requiring vasopressors. Or, oxygen requirement of low-flow nasal cannula[d] or blow-by.	Administer tocilizumab[b] 8 mg/kg intravenously 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.	Manage per guidance below, if no improvement within 24 hours of starting tocilizumab.

Grade 3	Temperature ≥100.4°F (38°C)[c] with either: Hypotension requiring one vasopressor, with or without vasopressin. Or, oxygen requirement of high-flow nasal cannula[d], facemask, non-rebreather mask, or Venturi mask	Administer tocilizumab 8 mg/kg intravenously 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.	If no improvement, administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours). Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days.
Grade 4	Temperature ≥100.4°F (38°C)[c] with either: Hypotension requiring multiple vasopressors (excluding vasopressin). Or, oxygen requirement of positive pressure (e.g., continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), intubation, and mechanical ventilation)	Administer tocilizumab 8 mg/kg intravenously 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.	As above or administer methylprednisolone 1000 mg intravenously per day for 3 days, per physician discretion. If no improvement or if condition worsens, consider alternate immunosuppressants.[b]

[a] Refer to tocilizumab prescribing information for details.

[b] Treat unresponsive CRS per institutional guidelines.

[c] Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as antipyretics or anticytokine therapy (e.g., tocilizumab or steroids).

[d] Low-flow nasal cannula is ≤6 L/min, and high-flow nasal cannula is >6 L/min.

[e] Based on American Society for Transplantation and Cellular Therapy (ASTCT) grading.

Neurologic toxicities

General management for neurologic toxicity (e.g., Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) with or without concurrent CRS) is summarized in Table 5.

At the first sign of neurologic toxicity including ICANS, consider neurology evaluation. Rule out other causes of neurologic symptoms. Provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities (see *Warnings and Precautions – Neurologic toxicities*). Withhold TECVAYLI® as indicated in Table 3.

Table 5: Recommendations for Management of Immune Effector Cell-Associated Neurotoxicity Syndrome

Grade	Presenting Symptoms[a]	Concurrent CRS	No Concurrent CRS
Grade 1	ICE score 7-9[b] or depressed level of consciousness[c]: awakens spontaneously.	Management of CRS per Table 4. Monitor neurologic symptoms and consider neurology consultation and evaluation, per physician discretion.	Monitor neurologic symptoms and consider neurology consultation and evaluation, per physician discretion.

		Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 2	ICE score 3-6[b] or depressed level of consciousness[c]: awakens to voice.	Administer tocilizumab per Table 4 for management of CRS. If no improvement after starting tocilizumab, administer dexamethasone[d] 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until resolution to Grade 1 or less, then taper.	Administer dexamethasone[d] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.
		Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed.	
Grade 3	ICE score 0-2[b] or depressed level of consciousness[c]: awakens only to tactile stimulus, or seizures[c], either: • any clinical seizure, focal or generalized, that resolves rapidly, or • non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, • or raised intracranial pressure: focal/local edema on neuroimaging[c].	Administer tocilizumab per Table 4 for management of CRS. In addition, administer dexamethasone[d] 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.	Administer dexamethasone[d] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper.
		Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed.	
Grade 4	ICE score-0[b] or depressed level of consciousness[c] either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures[c], either:	Administer tocilizumab per Table 4 for management of CRS. As above, or consider administration of methylprednisolone 1000 mg per day intravenously with first dose of tocilizumab, and continue methylprednisolone 1000 mg per day intravenously for 2 or more days.	As above, or consider administration of methylprednisolone 1000 mg per day intravenously for 3 days; if improves, then manage as above.

	• life-threatening prolonged seizure (>5 minutes), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings[c]: • deep focal motor weakness such as hemiparesis or paraparesis, or raised intracranial pressure/cerebral edema[c], with signs/symptoms such as: • diffuse cerebral edema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilledema, or • Cushing's triad.	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed. In case of raised intracranial pressure/cerebral edema, refer to local institutional guidelines for management.

[a] Management is determined by the most severe event, not attributable to any other cause.

[b] If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: **Orientation** (oriented to year, month, city, hospital = 4 points); **Naming** (name 3 objects, e.g., point to clock, pen, button = 3 points); **Following Commands** (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); **Writing** (ability to write a standard sentence = 1 point; and **Attention** (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.

[c] Attributable to no other cause.

[d] All references to dexamethasone administration are dexamethasone or equivalent

Special populations

Pediatrics

The safety and efficacy of TECVAYLI® have not been established in pediatric patients.

No data are available.

Elderly (65 years of age and older)

Of the 165 patients treated with TECVAYLI® in MajesTEC-1 at the recommended dose, 48% were 65 years of age or older, and 15% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

No dose adjustment is necessary (see *Pharmacokinetic Properties*).

Renal impairment

No formal studies of TECVAYLI® in patients with renal impairment have been conducted.

Based on population pharmacokinetic analyses, no dose adjustment is recommended for patients with mild or moderate renal impairment (see *Pharmacokinetic Properties*).

Hepatic impairment

No formal studies of TECVAYLI® in patients with hepatic impairment have been conducted.

Based on population pharmacokinetic analyses, no dose adjustment is recommended for patients with mild hepatic impairment (see *Pharmacokinetic Properties*).

Administration

It is very important that the instructions for preparation and administration provided in this section are strictly followed to minimize potential dosing errors with TECVAYLI® 10 mg/mL vial and TECVAYLI® 90 mg/mL vial.

TECVAYLI® should be administered via subcutaneous injection only. Do not administer TECVAYLI® intravenously.

TECVAYLI® should be administered by a healthcare professional with adequately trained medical personnel and appropriate medical equipment to manage severe reactions, including cytokine release syndrome (see *Warnings and Precautions - Cytokine Release Syndrome*).

TECVAYLI® 10 mg/mL vial and TECVAYLI® 90 mg/mL vial are supplied as ready-to-use solution for injection that do not need dilution prior to administration.

TECVAYLI® vials of different concentrations should not be combined to achieve treatment dose.

Use aseptic technique to prepare and administer TECVAYLI®.

Preparation of TECVAYLI®

- Verify the prescribed dose for each TECVAYLI® injection. To minimize errors, use the following tables to prepare TECVAYLI® injection.
    - Use Table 6 to determine total dose, injection volume and number of vials required based on patient's actual body weight for Step-up Dose 1 using TECVAYLI® 10 mg/mL.

Table 6: Injection Volumes of TECVAYLI® 10 mg/mL for Step-up Dose 1 (0.06 mg/kg)

	Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial=3 mL)
Step-Up Dose 1 (0.06 mg/kg)	35-39	2.2	0.22	1
	40-44	2.5	0.25	1
	45-49	2.8	0.28	1
	50-59	3.3	0.33	1
	60-69	3.9	0.39	1
	70-79	4.5	0.45	1
	80-89	5.1	0.51	1
	90-99	5.7	0.57	1
	100-109	6.3	0.63	1
	110-119	6.9	0.69	1

	120-129	7.5	0.75	1
	130-139	8.1	0.81	1
	140-149	8.7	0.87	1
	150-160	9.3	0.93	1

- Use Table 7 to determine total dose, injection volume and number of vials required based on patient's actual body weight for Step-up Dose 2 using TECVAYLI® 10 mg/mL.

Table 7: Injection Volumes of TECVAYLI® 10 mg/mL for Step-up Dose 2 (0.3 mg/kg)

	Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial=3 mL)
Step-up Dose 2 (0.3 mg/kg)	35-39	11	1.1	1
	40-44	13	1.3	1
	45-49	14	1.4	1
	50-59	16	1.6	1
	60-69	19	1.9	1
	70-79	22	2.2	1
	80-89	25	2.5	1
	90-99	28	2.8	1
	100-109	31	3.1	2
	110-119	34	3.4	2
	120-129	37	3.7	2
	130-139	40	4.0	2
	140-149	43	4.3	2
	150-160	47	4.7	2

- Use Table 8 to determine total dose, injection volume and number of vials required based on patient's actual body weight for the Treatment Dose using TECVAYLI® 90 mg/mL.

Table 8: Injection Volumes of TECVAYLI® 90 mg/mL for Treatment Dose (1.5 mg/kg)

	Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial=1.7 mL)
Treatment Dose (1.5 mg/kg)	35-39	56	0.62	1
	40-44	63	0.70	1
	45-49	70	0.78	1
	50-59	82	0.91	1
	60-69	99	1.1	1
	70-79	108	1.2	1
	80-89	126	1.4	1
	90-99	144	1.6	1
	100-109	153	1.7	1
	110-119	171	1.9	2

	120-129	189	2.1	2
	130-139	198	2.2	2
	140-149	216	2.4	2
	150-160	234	2.6	2

- Remove the appropriate strength TECVAYLI® vial from refrigerated storage [2°C–8°C (36°F–46°F)] and equilibrate to ambient temperature [15°C–30°C (59°F–86°F)], as needed, for at least 15 minutes. Do not warm TECVAYLI® in any other way.
- Once equilibrated, gently swirl the vial for approximately 10 seconds to mix. Do not shake.
- Withdraw the required injection volume of TECVAYLI® from the vial(s) into an appropriately sized syringe using a transfer needle.
    - Each injection volume should not exceed 2.0 mL. Divide doses requiring greater than 2.0 mL equally into multiple syringes.
- TECVAYLI® is compatible with stainless steel injection needles and polypropylene or polycarbonate syringe material.
- Replace the transfer needle with an appropriately sized needle for injection.
- Visually inspect TECVAYLI® for particulate matter and discoloration prior to administration. Do not use if the solution is discolored, or cloudy, or if foreign particles are present.
    - TECVAYLI® solution for injection is colorless to light yellow.

Administration of TECVAYLI®

- Inject the required volume of TECVAYLI® into the subcutaneous tissue of the abdomen (preferred injection site). Alternatively, TECVAYLI® may be injected into the subcutaneous tissue at other sites (e.g., thigh). If multiple injections are required, TECVAYLI® injections should be at least 2 cm apart.
- Do not inject into tattoos or scars or areas where the skin is red, bruised, tender, hard or not intact.
- Any unused medicinal product or waste material should be disposed in accordance with local requirements.

Storage

- The prepared syringes should be administered immediately. If immediate administration is not possible, in-use storage times of the prepared syringe should be no longer than 20 hours at 2°C - 8°C or ambient temperature (15°C - 30°C). Discard after 20 hours, if not used.

Monitoring

- Instruct patients to remain within proximity of a healthcare facility and monitor patients daily for 48 hours for signs and symptoms of CRS after administration of all doses within the TECVAYLI® step-up dosing schedule (see Table 1 and *Dosage and Administration- Management of severe adverse reactions* and *Warnings and Precautions - Cytokine Release Syndrome*).

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in *List of Excipients*.

Warnings and Precautions

The data described in the Warnings and Precautions reflects the safety profile of 165 patients with relapsed or refractory multiple myeloma who received the recommended dose regimen of subcutaneous TECVAYLI® monotherapy in MajesTEC-1, unless otherwise noted.

Cytokine release syndrome (CRS)

Cytokine release syndrome (CRS), including life-threatening or fatal reactions, may occur in patients receiving TECVAYLI®. The majority of CRS events observed following TECVAYLI® administration were Grade 1 and Grade 2 (see *Adverse Reactions*). The median time to onset of CRS was 2 (Range: 1 to 6) days after the most recent dose with a median duration of 2 (Range: 1 to 9) days.

Clinical signs and symptoms of CRS may include, but are not limited to, fever, chills, hypotension, tachycardia, hypoxia, headache, and elevated liver enzymes. Potentially life-threatening complications of CRS may include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation (DIC).

Initiate therapy according to TECVAYLI® step-up dosing schedule to reduce risk of CRS (see Table 1). Failure to follow the recommended doses or dosing schedule for initiation of therapy or re-initiation of therapy after dose delays may result in increased frequency and severity of adverse events related to mechanism of action. Administer pretreatment medications (corticosteroids, antihistamine, and antipyretics) prior to each dose of the TECVAYLI® step-up dosing schedule to reduce risk of CRS and monitor patients following administration accordingly (see *Dosage and Administration - Pretreatment medications* and *Dosage and Administration - Administration*). In patients who experienced CRS following their previous dose, administer pretreatment medications prior to the next dose of TECVAYLI®.

The following patients should be instructed to remain within proximity of a healthcare facility and monitored daily for 48 hours:

- If the patient has received any dose within the TECVAYLI® step-up dosing schedule (for CRS).
- If the patient has received TECVAYLI® after experiencing Grade 2 or higher CRS.

Counsel patients to seek medical attention should signs or symptoms of CRS occur. At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with

supportive care, tocilizumab and/or corticosteroids, based on severity as indicated in Table 4. In MajesTEC-1, tocilizumab, corticosteroids, and tocilizumab in combination with corticosteroids were used to treat 32%, 11% and 3% of CRS events, respectively. The use of myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor (GM-CSF), should be avoided during CRS. Withhold treatment with TECVAYLI® until CRS resolves as indicated in Table 3 (see *Dosage and Administration - Management of severe adverse reactions*).

Neurologic toxicities

Serious or life-threatening neurologic toxicities, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), may occur following treatment with TECVAYLI® The majority of neurologic toxicity events were Grade 1 and Grade 2 (see *Adverse Reactions*). The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.

With longer follow up, Grade 4 seizure (one patient) occurred in patients who received TECVAYLI®.

Monitor patients for signs or symptoms of neurologic toxicities during treatment and treat promptly.

Counsel patients to seek medical attention should signs or symptoms of neurologic toxicity occur. At the first sign of neurologic toxicity, including ICANS, immediately evaluate patient and institute treatment based on severity as indicated in Table 5 (see *Dosage and Administration - Management of severe adverse reactions*). Patients who experience Grade 2 or higher ICANS or first occurrence of Grade 3 ICANS with the previous dose of TECVALI® should be instructed to remain within proximity of a healthcare facility and monitored for signs and symptoms daily for 48 hours.

For ICANS or other neurologic toxicities, withhold treatment with TECVAYLI® as indicated in Table 3 and manage adverse reactions based on recommendations in Table 5.

Due to the potential for ICANS, patients should be advised not to drive or operate heavy machinery during the TECVAYLI® step-up dosing schedule and for 48 hours after completing the TECVAYLI® step-up dosing schedule and in the event of new onset of any neurological symptoms (see *Effects on Ability to Drive and Use Machines*).

Infections

Severe, life-threatening or fatal infections have been reported in patients receiving TECVAYLI® (see *Adverse Reactions*). New or reactivated viral infections occurred during therapy with TECVAYLI®.

Monitor patients for signs and symptoms of infection prior to and during treatment with TECVAYLI® and treat appropriately. Prophylactic antimicrobials should be administered according to local institutional guidelines.

TECVAYLI® step-up dosing schedule should not be administered in patients with active infection. Withhold treatment with TECVAYLI® as indicated in Table 3 (see *Dosage and Administration - Dosage modifications*).

Progressive Multifocal Leukoencephalopathy (PML), which can be fatal, has also been reported in patients receiving TECVAYLI®. Monitor any new onset of or changes in pre-existing neurological signs or symptoms. If PML is suspected, withhold treatment with TECVAYLI® and initiate appropriate diagnostic testing. Discontinue TECVAYLI® if PML is confirmed.

Hepatitis B Virus reactivation

Hepatitis B virus reactivation can occur in patients treated with drugs directed against B cells, and in some cases, may result in fulminant hepatitis, hepatic failure, and death.

Patients with evidence of positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation while receiving TECVAYLI®, and for at least six months following the end of treatment.

In patients who develop reactivation of HBV while on TECVAYLI®, withhold treatment with TECVAYLI® as indicated in Table 3 and manage per local institutional guidelines (see *Dosage and Administration – Dosage modifications*).

Hypogammaglobulinemia

Hypogammaglobulinemia has been reported in patients receiving TECVAYLI® (see *Adverse Reactions*).

Monitor immunoglobulin levels during treatment with TECVAYLI® and treat according to local institutional guidelines, including infection precautions, antibiotic or antiviral prophylaxis, and administration of immunoglobulin replacement therapy.

Vaccines

Immune response to vaccines may be reduced when taking TECVAYLI®.

The safety of immunization with live viral vaccines during or following TECVAYLI® treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 4 weeks prior to the start of treatment, during treatment, and at least 4 weeks after treatment.

Neutropenia

Neutropenia and febrile neutropenia have been reported in patients who received TECVAYLI® (see *Adverse Reactions*).

Monitor complete blood cell counts at baseline and periodically during treatment and provide supportive care per local institutional guidelines.

Patients with neutropenia should be monitored for signs of infection.

Withhold treatment with TECVAYLI® based on severity as indicated in Table 3 (see *Dosage and Administration - Dosage modifications*).

Interactions

No drug interaction studies have been performed with TECVAYLI®.

The initial release of cytokines associated with the start of TECVAYLI® treatment could suppress CYP450 enzymes. Based on physiologically based pharmacokinetic (PBPK) modeling, the highest risk of drug-drug interaction is predicted to be from initiation of TECVAYLI® step-up dosing schedule up to 7 days after the first Treatment Dose or during a CRS event. During this time period, monitor for toxicity or drug concentrations (e.g., cyclosporine) in patients who are receiving concomitant CYP450 substrates with a narrow therapeutic index. The dose of the concomitant drug should be adjusted as needed.

Pregnancy, Breast-feeding and Fertility

Pregnancy

There are no available data on the use of TECVAYLI® in pregnant women or animal data to assess the risk of TECVAYLI® in pregnancy. Human IgG is known to cross the placenta after the first trimester of pregnancy. Therefore, teclistamab has the potential to be transmitted from the mother to the developing fetus. TECVAYLI® is not recommended for women who are pregnant. TECVAYLI® is associated with hypogammaglobulinemia, therefore, assessment of immunoglobulin levels in newborns of mothers treated with TECVAYLI® should be considered.

Breast-feeding

It is not known whether teclistamab is excreted in human or animal milk, affects breastfed infants or affects milk production. Because of the potential for serious adverse reactions in breastfed infants from TECVAYLI®, advise patients not to breastfeed during treatment with TECVAYLI® and for at least five months after the last dose.

Females and males of reproductive potential

Pregnancy testing

Pregnancy status for females of child-bearing potential should be verified prior to starting treatment with TECVAYLI®.

Contraception

Advise females of reproductive potential to use effective contraception during treatment and for five months after the final dose of TECVAYLI®.

Advise male patients with a female partner of reproductive potential to use effective contraception during treatment and for three months after the last dose of TECVAYLI®.

Fertility

There are no data on the effect of TECVAYLI® on fertility. Effects of TECVAYLI® on male and female fertility have not been evaluated in animal studies.

Effects on Ability to Drive and Use Machines

Due to the potential for ICANS, patients receiving TECVAYLI® are at risk of depressed level of consciousness. Patients should avoid driving or operating heavy or potentially dangerous machinery during and for 48 hours after completion of TECVAYLI® step-up dosing schedule and in the event of new onset of any neurological symptoms (Table 1) (see *Dosage and Administration*).

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of teclistamab based on the comprehensive assessment of the available adverse event information. A causal relationship with teclistamab cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety data of TECVAYLI® was evaluated in MajesTEC-1, which included 165 adult patients with relapsed or refractory multiple myeloma who received the recommended dose regimen of subcutaneous TECVAYLI® as monotherapy. The median duration of TECVAYLI® treatment was 8.5 (Range: 0.2 to 24.4) months.

The most frequent adverse reactions of any grade (≥20%) in patients, excluding laboratory abnormalities, were hypogammaglobulinemia (75%), cytokine release syndrome (72%), musculoskeletal pain (52%), fatigue (41%), injection site reaction (38%), upper respiratory tract infection (37%), diarrhea (29%), pneumonia (28%), nausea (27%), pyrexia (27%), headache (24%), cough (24%), constipation (21%) and pain (21%).

Serious adverse reactions were reported in 65% patients who received TECVAYLI®. Serious adverse reactions reported in ≥2% of patients included pneumonia (16%), COVID-19 (15%), cytokine release syndrome (8%), sepsis (7%), pyrexia (5.0%), musculoskeletal pain (5.0%), acute kidney injury (4.8%), diarrhea (3.0%), cellulitis (2.4%), hypoxia (2.4%), febrile neutropenia (2.4%), and encephalopathy (2.4%).

Dose interruptions (dose delays and dose skips) of TECVAYLI® due to adverse reactions occurred in 65% of patients. The most frequent adverse reactions (≥5%) leading to dose interruptions were neutropenia (26%), COVID-19 (12%), pneumonia (10%), cytokine release syndrome (8%), and pyrexia (7%).

Dose reduction of TECVAYLI® due to adverse reaction occurred in one patient (0.6%) due to neutropenia.

Permanent discontinuation of TECVAYLI® due to adverse reactions occurred in two patients (1.2%), both due to infections.

Table 9 lists adverse reactions reported in ≥10% of patients who received TECVAYLI® in MajesTEC-1.

Table 9: Adverse Reactions (≥10%) in Patients with Multiple Myeloma Treated with TECVAYLI® in MajesTEC-1

System Organ Class	Adverse Reaction	N=165 n (%)	
		Any Grade	Grade 3 or 4
Gastrointestinal disorders	Diarrhea	47 (29%)	6 (3.6%)
	Nausea	45 (27%)	1 (0.6%)
	Constipation	34 (21%)	0
	Vomiting	21 (13%)	1 (0.6%)
General disorders and administration site conditions	Fatigue[1]	67 (41%)	5 (3.0%)
	Injection site reaction[2]	62 (38%)	1 (0.6%)
	Pyrexia	45 (27%)	1 (0.6%)
	Pain[3]	34 (21%)	3 (1.8%)
	Edema[4]	23 (14%)	0
Immune system disorders	Hypogammaglobulinemia[5]	123 (75%)	3 (1.8%)
	Cytokine release syndrome	119 (72%)	1 (0.6%)
Infections and infestations	Upper respiratory tract infection[6]	61 (37%)	4 (2.4%)
	Pneumonia[7]	46 (28%)	32 (19%)
	COVID-19[8]	30 (18%)	20 (12%)
Metabolism and nutrition disorders	Decreased appetite	20 (12%)	1 (0.6%)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[9]	85 (52%)	14 (9%)
Nervous system disorders	Headache	39 (24%)	1 (0.6%)
	Neuropathy peripheral[10]	26 (16%)	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	Cough[11]	39 (24%)	0
	Dyspnea[12]	22 (13%)	3 (1.8%)
Vascular disorders	Hypertension[13]	21 (13%)	9 (6%)
	Hemorrhage[14]	20 (12%)	5 (3.0%)

Adverse events are coded using MedDRA Version 24.0.

1 Fatigue includes asthenia, fatigue and malaise.

2 Injection site reaction includes injection site bruising, injection site cellulitis, injection site discomfort, injection site erythema, injection site hematoma, injection site induration, injection site inflammation, injection site edema, injection site pruritus, injection site rash, injection site reaction and injection site swelling.

3 Pain includes ear pain, flank pain, groin pain, non-cardiac chest pain, oropharyngeal pain, pain, pain in jaw, toothache and tumor pain.

4 Edema includes face edema, fluid overload, edema peripheral and peripheral swelling.

5 Hypogammaglobulinemia includes patients with adverse events of hypogammaglobulinemia, hypoglobulinemia; immunoglobulins decreased; and/or patients with laboratory IgG levels below 500 mg/dL following treatment with teclistamab.

6 Upper respiratory tract infection includes bronchitis, nasopharyngitis, pharyngitis, respiratory tract infection, respiratory tract infection bacterial, rhinitis, rhinovirus infection, sinusitis, tracheitis, upper respiratory tract infection and viral upper respiratory tract infection.

7 Pneumonia includes Enterobacter pneumonia, lower respiratory tract infection, lower respiratory tract infection viral, Metapneumovirus pneumonia, Pneumocystis jirovecii pneumonia, pneumonia, Pneumonia adenoviral, Pneumonia bacterial, Pneumonia klebsiella, Pneumonia moraxella, Pneumonia pneumococcal, Pneumonia pseudomonal, Pneumonia respiratory syncytial viral, Pneumonia staphylococcal and Pneumonia viral.

8 COVID-19 includes asymptomatic COVID-19 and COVID-19.

9 Musculoskeletal pain includes arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain and pain in extremity.

10 Neuropathy peripheral includes dysesthesia, hypoesthesia, hypoesthesia oral, neuralgia, paresthesia, paresthesia oral, peripheral sensory neuropathy and sciatica.

11 Cough includes allergic cough, cough, productive cough and upper-airway cough syndrome.

12 Dyspnea includes acute respiratory failure, dyspnea and dyspnea exertional.

13 Hypertension includes essential hypertension and hypertension.

14 Hemorrhage includes conjunctival hemorrhage, epistaxis, hematoma, hematuria, hemoperitoneum, hemorrhoidal hemorrhage, lower gastrointestinal hemorrhage, melaena, mouth hemorrhage and subdural hematoma.

Table 10 lists other clinically relevant adverse reactions reported in <10% of patients who received TECVAYLI® in MajesTEC-1.

Table 10: Adverse Reactions (<10%) in Patients with Multiple Myeloma Treated with TECVAYLI® in MajesTEC-1

		N=165	
		n (%)	
System Organ Class	**Adverse Reaction**	**Any Grade**	**Grade 3 or 4**
Infections and infestations	Sepsis[1]	13 (7.9%)	11 (6.7%)
	Cellulitis	7 (4.2%)	5 (3.0%)
Blood and lymphatic system disorders	Febrile neutropenia	6 (3.6%)	5 (3.0%)
Nervous system disorders	Encephalopathy[2]	16 (9.7%)	0
	Immune effector cell-associated neurotoxicity syndrome	5 (3.0%)	0
	Tremor	5 (3.0%)	0
Respiratory, thoracic and mediastinal disorders	Hypoxia	16 (9.7%)	6 (3.6%)

Adverse events are coded using MedDRA Version 24.0.

1 Sepsis includes bacteremia, Meningococcal sepsis, neutropenic sepsis, Pseudomonal bacteremia, Pseudomonal sepsis, sepsis and Staphylococcal bacteremia.

2 Encephalopathy includes confusional state, depressed level of consciousness, lethargy, memory impairment and somnolence.

Table 11 lists laboratory abnormalities that worsened from baseline in patients who received TECVAYLI® in MajesTEC-1. The most frequent Grade 3 or 4 laboratory abnormalities (≥20%)

were decreased lymphocytes, decreased neutrophil, decreased white blood cells, decreased hemoglobin and decreased platelets.

Table 11: Laboratory Abnormalities Worsening from Baseline in at least 20% of Patients with Multiple Myeloma Treated with TECVAYLI® in MajesTEC-1

	N=165	
	n (%)	
Laboratory Abnormality	**Any Grade**	**Grade 3 or 4**
Lymphocyte count decreased	151 (92%)	137 (83%)
White blood cell decreased	147 (89%)	72 (44%)
Neutrophil count decreased	143 (87%)	104 (63%)
Platelet count decreased	120 (73%)	38 (23%)
Hypoalbuminemia	118 (72%)	10 (6%)
Anemia	117 (71%)	61 (37%)
Alkaline phosphatase increased	71 (43%)	5 (3.0%)
Hypophosphatemia	71 (43%)	24 (15%)
Aspartate aminotransferase increased	67 (41%)	5 (3.0%)
Gamma-glutamyltransferase increased	63 (38%)	15 (9%)
Hyponatremia	59 (36%)	20 (12%)
Alanine aminotransferase increased	57 (35%)	7 (4.2%)
Hypocalcemia (Corrected)	57 (35%)	3 (1.8%)
Creatinine increased	56 (34%)	5 (3.0%)
Hypokalemia	51 (31%)	8 (4.8%)
Hypomagnesemia	47 (28%)	0
Hypercalcemia (Corrected)	46 (28%)	7 (4.2%)
Lipase increased	42 (25%)	9 (5%)
Serum amylase increased	39 (24%)	7 (4.2%)
Hyperkalemia	33 (20%)	3 (1.8%)

Laboratory toxicity grades are derived based on the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.

Description of selected adverse reactions

Cytokine release syndrome

In Majes-TEC-1 (N=165), CRS was reported in 72% of patients following treatment with TECVAYLI®. One-third (33%) of patients experienced more than one CRS event. Most patients experienced CRS following Step-up Dose 1 (44%), Step-up Dose 2 (35%), or the initial treatment dose (24%). Less than 3% of patients developed first occurrence of CRS following subsequent doses of TECVAYLI®. Most CRS events were Grade 1 (50%) and Grade 2 (21%). Less than one percent (0.6%) of CRS events were Grade 3, and no Grade 4 or fatal events occurred. The median time to onset of CRS was 2 (Range: 1 to 6) days after the most recent dose, with a median duration of 2 (Range: 1 to 9) days.

The most frequent (≥3%) signs and symptoms associated with CRS were fever (72%), hypoxia (13%), chills (12%), hypotension (12%), sinus tachycardia (7%), headache (7%), and elevated liver enzymes (aspartate aminotransferase and alanine aminotransferase elevation) (3.6% each).

Neurologic toxicities

In Majes-TEC-1 (N=165), neurologic toxicities were reported in 15% of patients receiving TECVAYLI®. Most neurologic toxicity events were Grade 1 (8.5%),Grade 2 (5.5%) and Grade 4 (0.6%). The most frequently reported neurologic toxicity was headache (8.5%).

ICANS was reported in 3% of patients receiving TECVAYLI® at the recommended dose. The most frequent clinical manifestations of ICANS reported were confusional state (1.2%) and dysgraphia (1.2%). The median time to onset of ICANS was 4 (Range: 2 to 5) days after the most recent dose, with a median duration of 3 (Range: 1 to 20) days.

Overdose

Symptoms and signs

The maximum tolerated dose of teclistamab has not been determined. In clinical trials, doses of up to 6 mg/kg have been administered.

Treatment

In the event of an overdose, the patient should be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment should be instituted immediately.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: TBD, ATC code: TBD.

Mechanism of action

Teclistamab is a full-size, IgG4-PAA bispecific antibody that targets the CD3 receptor expressed on the surface of T cells and B cell maturation antigen (BCMA), which is expressed on the surface of malignant multiple myeloma B-lineage cells, as well as late-stage B cells and plasma cells. With its dual binding sites, teclistamab is able to draw $CD3^+$ T cells in close proximity to $BCMA^+$ cells, resulting in T cell activation and subsequent lysis and death of $BCMA^+$ cells, which is mediated by secreted perforin and various granzymes stored in the secretory vesicles of cytotoxic T cells. This effect occurs without regard to T cell receptor specificity or reliance on major histocompatibility complex (MHC) Class 1 molecules on the surface of antigen presenting cells.

Pharmacodynamic effects

Within the first month of treatment with teclistamab, activation and redistribution of T-cells, reduction of B-cells and induction of serum cytokines were observed.

Within one month, the majority of responders had reduction in soluble BCMA, and a greater reduction in soluble BCMA was observed in patients with deeper responses to teclistamab.

Immunogenicity

Patients treated with subcutaneous teclistamab monotherapy (N=238) in MajesTEC-1 were evaluated for antibodies to teclistamab using an electrochemiluminescence-based immunoassay. One patient (0.4%) developed antibodies to teclistamab of low-titer which were neutralizing.

Effect on QT/QTc interval and cardiac electrophysiology

At the recommended treatment dose (1.5 mg/kg) of TECVAYLI®, no clinically relevant QTc prolongation has been observed.

Clinical studies

The efficacy of TECVAYLI® monotherapy was evaluated in patients with relapsed or refractory multiple myeloma in a single-arm, open-label, multicenter, Phase 1/2 study (MajesTEC-1). The study included patients who had previously received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. The study excluded patients who experienced stroke or seizure within the past 6 months and patients with Eastern Cooperative Oncology Group performance score (ECOG PS) ≥2, plasma cell leukaemia, known active CNS involvement or exhibited clinical signs of meningeal involvement of multiple myeloma, or active or documented history of autoimmune disease, with the exception of vitiligo, Type 1 diabetes and prior autoimmune thyroiditis.

Patients received initial step-up doses of 0.06 mg/kg and 0.3 mg/kg of TECVAYLI® administered subcutaneously followed by the treatment dose of TECVAYLI® 1.5 mg/kg administered subcutaneously once weekly thereafter until disease progression or unacceptable toxicity (see *Dosage and Administration - Dosage – Adults*). The median duration between Step-up Dose 1 and Step-up Dose 2 was 2.9 (Range: 2-7) days. The median duration between Step-up Dose 2 and the initial treatment dose was 3.9 (Range: 2-9) days. Patients were hospitalized for monitoring for at least 48 hours after administration of each dose of the TECVAYLI® step-up dosing schedule.

The efficacy population included 150 patients. The median age was 64.5 (Range: 33-84) years with 15% of patients ≥75 years of age; 59% were male; 89% were White, 4% were Black, 2% were Asian. The International Staging System (ISS) at study entry was 53% in Stage I, 35% in Stage II, and 11% in Stage III. High-risk cytogenetics (presence of del(17p). t(4;14) or t(14; 16)) were present in 27% of patients. Eighteen percent of patients had extramedullary plasmacytomas.

The median time since initial diagnosis of multiple myeloma to enrollment was 6.1 (Range: 0.8-22.7) years. The median number of prior therapies was 5 (Range: 2-14) with 21% of patients who received 3 prior lines of therapy. Eighty-two percent of patients received prior stem cell transplantation. All patients had received prior therapy with a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, and 77% were triple-class refractory (refractory to PI, an IMiD agent and an anti-CD38 monoclonal antibody).

Efficacy results were based on overall response rate as determined by the Independent Review Committee (IRC) assessment using International Myeloma Working Group (IMWG) 2016 criteria (see Table 12).

Table 12: Efficacy Results for MajesTEC-1

	N=150
Overall response rate (ORR: sCR+CR+VGPR+PR) n(%)	94 (63%)
95% CI (%)	(54.4%, 70.4%)
Stringent complete response (sCR)	38 (25%)
Complete response (CR)	10 (7%)
Very good partial response (VGPR)	40 (27%)
Partial response (PR)	6 (4%)
Duration of Response (DOR) (months)	
Number of responders DOR (Months): Median (95% CI)	94 NE (11.5, NE)
Time to First Response (months)	
Number of responders Median Range	94 1.2 (0.2; 5.5)

NE=not estimable

Response durations were longer in patients who achieved a CR or better as compared to patients with VGPR. Of the 48 patients who achieved a CR or better, it is estimated that 83% (95% CI: 64.9%, 92.5%) had a remission lasting at least 12 months. The median duration of response for patients with VGPR (n=40) was 11.5 months (95% CI: 9.0, NE).

In patients completing the EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 Item) (N=55) after approximately 20 weeks of therapy with TECVAYLI®, improvement from baseline in global health status (N=54) and pain scores were reported and baseline scores in fatigue and physical function were maintained. The results of the patient-reported outcomes should be interpreted with caution considering the open-label, single-arm design of the study.

Pharmacokinetic Properties

Teclistamab exhibited approximately dose-proportional pharmacokinetics following subcutaneous administration across a dose range of 0.08 mg/kg to 3 mg/kg (0.05 to 2.0 times the recommended dose). The mean accumulation ratio following 1.5 mg/kg subcutaneous weekly dosing of teclistamab at the 7th weekly treatment dose was 2.71- and 3.05-fold for C_{max} and AUC_{tau}, respectively. The mean bioavailability following teclistamab subcutaneous administration was 69% relative to intravenous dosing.

Pharmacokinetic parameters of teclistamab following the 1st and 7th recommended treatment dose of 1.5 mg/kg are shown in Table 13.

Table 13: Pharmacokinetic Parameters of Teclistamab Following the First and Seventh Recommended Treatment Dose (1.5 mg/kg) in Patients with Relapsed or Refractory Multiple Myeloma [MajesTEC-1]

Pharmacokinetic Parameters	**The 1st Treatment Dose of 1.5 mg/kg**	**The 7th Treatment Dose of 1.5 mg/kg**
T_{max} (hours)	72.0 (45.8 – 193) (n=40)	48.9 (0.0 – 166) (n=15)

C_{max} (µg/mL)	8.74 ± 3.65 (n=40)	25.3 ± 11.1 (n=15)
C_{trough} (µg/mL)	7.67 ± 3.52 (n=38)	22.1 ± 10.9 (n=27)
AUC_{tau} (µg·h/mL)	1169 ± 481 (n=38)	3905 ± 1748 (n=13)

T_{max} = Time to reach the C_{max}; C_{max} = Maximum observed serum teclistamab concentration; C_{trough} = Observed serum teclistamab concentration prior to next dose; AUC_{tau} = Area under the concentration-time curve over the weekly dosing interval. Data are presented as mean ± standard deviation, except for T_{max} which is presented as median (minimum, maximum).

Distribution

Based on the population pharmacokinetic model, mean volume of distribution was 5.63L (29% coefficient of variation (CV)).

Excretion

Population pharmacokinetic analysis showed that teclistamab clearance decreases over time, with a mean (CV%) maximal reduction from baseline to the 13th treatment dose of 40.8% (56%). The geometric mean (CV%) clearance is 0.472 L/day (64%) at the 13th treatment dose. Patients who discontinue teclistamab after the 13th treatment dose are expected to have a 50% reduction from C_{max} in teclistamab concentration at a median (5th to 95th percentile) time of 15 (7 to 33) days after T_{max} and a 97% reduction from C_{max} in teclistamab concentration at a median time of 69 (32 to 163) days after T_{max}.

Population pharmacokinetic analysis (based on MajesTEC-1) showed that soluble BCMA did not impact teclistamab serum concentrations.

Special populations

Age and sex

The pharmacokinetics of TECVAYLI® in pediatric patients have not been investigated.

Results of population pharmacokinetic analyses indicate that age (24 to 84 years) and sex did not influence the pharmacokinetics of teclistamab.

Renal impairment

No formal studies of TECVAYLI® in patients with renal impairment have been conducted.

Results of population pharmacokinetic analyses indicate that mild renal impairment (60 mL/min/1.73 m^2 ≤ estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73 m^2) or moderate renal impairment (30 mL/min/1.73m^2 ≤ eGFR <60mL/min/1.73 m^2) did not significantly influence the pharmacokinetics of teclistamab. Limited data are available from patients with severe renal impairment.

Hepatic impairment

No formal studies of TECVAYLI® in patients with hepatic impairment have been conducted.

Results of population pharmacokinetic analyses indicate that mild hepatic impairment (total bilirubin >1 to 1.5 times upper limit of normal (ULN) and any aspartate aminotransferase (AST), or total bilirubin ≤ULN and AST>ULN) did not significantly influence the pharmacokinetics of teclistamab. No data are available in patients with moderate and severe hepatic impairment.

NON-CLINICAL INFORMATION

Based on the expression of BCMA, teclistamab specifically targets $BCMA^+$ cells, thus reducing potential off-target effects toward other cell lineages.

Carcinogenicity and Mutagenicity

No genotoxicity or carcinogenicity studies have been performed to assess the carcinogenic or genotoxic potential of teclistamab.

Reproductive Toxicology

No reproductive and developmental toxicity animal studies have been conducted to evaluate the potential effects of teclistamab.

Fertility

No studies have been conducted to evaluate the effects of teclistamab on fertility in males or females. In the 5-week repeat-dose toxicity study in cynomolgus monkeys, there were no notable effects in the male and female reproductive organs at doses up to 30 mg/kg/week (approximately 22 times the maximum recommended human dose based on AUC exposure) intravenously for five weeks.

PHARMACEUTICAL INFORMATION

List of Excipients

10 mg/mL vial and 90 mg/mL vial

EDTA disodium salt dihydrate
Glacial acetic acid
Polysorbate 20
Sodium acetate trihydrate
Sucrose
Water for injection

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf Life

Unopened vial:
See expiry date on the outer pack.

Prepared syringe:
The prepared syringes should be administered immediately. If immediate administration is not possible, in-use storage times of the prepared syringe should be no longer than 20 hours at 2°C – 8°C or ambient temperature (15°C – 30°C). Discard after 20 hours if not used.

Storage Conditions

10 mg/mL vial and 90 mg/mL vial

Store refrigerated at 2°C to 8°C.

Do not shake.

Store in the original carton in order to protect from light.

Do not freeze.

Keep out of the sight and reach of children.

Nature and Contents of Container

3 mL solution for injection in a Type 1 glass vial with an elastomeric closure and aluminum seal with a flip off button containing 30 mg of sterile teclistamab (10 mg/mL). Pack size of 1 vial.

1.7 mL solution for injection in a Type 1 glass vial with an elastomeric closure and aluminum seal with a flip off button containing 153 mg of sterile teclistamab (90 mg/mL). Pack size of 1 vial.

Instructions for Use and Handling and Disposal

Any unused medicinal product or waste material should be disposed in accordance with local requirements.

BATCH RELEASER

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