Teclistamab (Tecvayli®) as monotherapy for the treatment of patients with relapsed and refractory multiple myeloma (MM) who have received at least three prior therapies

General information

Drug description [1]	Indication [2]
Teclistamab (JNJ-64007957, Tecvayli®) is a monoclonal antibody that targets two proteins at the same time: a protein called B-cell maturation antigen (BCMA), which is present on the surface of the MM cells, and CD_3, a protein that is present on T cells (cells of the immune system responsible for destroying abnormal cells). By attaching to BCMA and CD_3 at the same time, the medicine activates the T cells to kill the MM cells.	Teclistamab (Tecvayli®) is indicated as monotherapy for the treatment of adult patients with relapsed and refractory MM, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

Current treatment [3]

- Treatment for relapsed MM depends on how long the patient was in remission for; the previous treatment received and the general health of the patient.
- Treatment options usually involve the use of targeted cancer drugs; a combination of chemotherapy drugs, with or without targeted cancer drugs; and a steroid.
- NICE guidelines recommend the following treatment options for relapsed or refractory MM:
  - Ixazomib, with lenalidomide and dexamethasone is recommended for patients who have already received 2 or 3 lines of therapy.
  - Panobinostat in combination with bortezomib and dexamethasone is recommended for adult patients with relapsed and/or refractory MM who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent.
  - Lenalidomide in combination with dexamethasone is recommended in people who have received 2 or more prior therapies.
  - Isatuximab, plus pomalidomide and dexamethasone, is recommended for relapsed and refractory MM in adults who have had lenalidomide and a proteasome inhibitor, and whose disease has progressed on their last treatment, only if they have had 3 previous lines of treatment.
  - Daratumumab monotherapy is recommended for treating relapsed and refractory MM in adults whose previous therapy included a proteasome inhibitor and an immunomodulator, and whose disease progressed on the last therapy, only if they have daratumumab after 3 previous therapies.
  - Pomalidomide, in combination with low-dose dexamethasone, is recommended for treating MM in adults at third or subsequent relapse; that is, after 3 previous treatments including both lenalidomide and bortezomib.

Regulatory status

EMA [1]

Approval status for this indication: On 21 July 2022, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Tecvayli®.

UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 23/08/2022

The full indication is:

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

Other indications: none

FDA [5]

Approval status for this indication: not approved

In December 2021, a biologics license application has been submitted to the FDA for teclistamab as treatment of patients with relapsed or refractory MM [5].

On 25 October 2022, the FDA granted accelerated approval to teclistamab-cqyv (Tecvayli®), the first bispecific BCMA-directed CD_3 T-cell engager, for adult patients with relapsed or refractory multiple myeloma who have received at least **four** prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody [6].

Other indications: none

✓ Medicine received a conditional marketing authorisation[1] ✓ Accelerated assessment[2]	

Pre-treatment [7]

- ❖ The following pre-treatment medicinal products must be administered 1 to 3 hours before each dose of the Tecvayli® step-up dosing schedule (see Product Information) to reduce the risk of cytokine release syndrome
  - Corticosteroid (oral or intravenous dexamethasone 16 mg)
  - Antihistamine (oral or intravenous diphenhydramine 50 mg, or equivalent)
  - Antipyretics (oral or intravenous acetaminophen 650 to 1 000 mg, or equivalent)
- ❖ Administration of pre-treatment medicinal products may also be required prior to administration of subsequent doses of Tecvayli® for the following patients:
  - Patients who repeat doses within the Tecvayli® step-up dosing schedule due to dose delays, or
  - Patients who experienced CRS following the previous dose.
- ❖ Prevention of herpes zoster reactivation
  - Prior to starting treatment with Tecvayli®, antiviral prophylaxis should be considered for the prevention of herpes zoster virus reactivation, per local institutional guidelines.

Special warnings and precautions for use [7]

- ❖ Traceability
  - In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.
- ❖ Cytokine release syndrome (CRS)
  - CRS, including life-threatening or fatal reactions, may occur in patients receiving Tecvayli®. Clinical signs and symptoms of CRS may include but are not limited to fever, hypoxia, chills, hypotension, tachycardia, 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.
  - Treatment should be initiated with Tecvayli according to the step-up dosing schedule to reduce risk of CRS. Pre-treatment medicinal products (corticosteroids, antihistamine and antipyretics) should be administered prior to each dose of the Tecvayli® step-up dosing schedule to reduce risk of CRS (see product information).
  - 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.
  - Patients who experience CRS following their previous dose should be administered pre-treatment medicinal products prior to the next dose of Tecvayli®.
  - Patients should be counselled to seek medical attention should signs or symptoms of CRS occur. At the first sign of CRS, patients should be immediately evaluated for hospitalisation. Treatment with supportive care, tocilizumab and/or corticosteroids should be instituted, based on severity as indicated (see product information).
  - The use of myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor, has the potential to worsen CRS symptoms and should be avoided during CRS. Treatment with Tecvayli® should be withheld until CRS resolves as indicated (see product information).
  - Management of cytokine release syndrome
    - CRS should be identified based on clinical presentation. Patients should be evaluated and treated for other causes of fever, hypoxia, and hypotension. If CRS is suspected, Tecvayli® should be withheld until the adverse reaction resolves (see product information).
    - CRS should be managed according to the recommendations in the product information. Supportive care for CRS (including but not limited to anti-pyretic agents, intravenous fluid support, vasopressors, supplemental oxygen, etc.) should be administered as appropriate. Laboratory testing to monitor for disseminated intravascular coagulation (DIC), haematology parameters, as well as pulmonary, cardiac, renal, and hepatic function should be considered.
- ❖ Neurologic toxicities
  - Serious or life-threatening neurologic toxicities, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) may occur following treatment with Tecvayli®.
  - Patients should be monitored for signs or symptoms of neurologic toxicities during treatment and treated promptly. Patients should be counselled to seek medical attention should signs or symptoms of neurologic toxicity occur. At the first sign of neurologic toxicity, including ICANS, patients should be immediately evaluated and treated based on severity. Patients who experience Grade 2 or higher

[1] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.
[2] This medicine had an accelerated assessment, meaning that it is a medicine of major interest for public health, so its timeframe for review was 150 evaluation days rather than 210.

ICANS or first occurrence of Grade 3 ICANS with the previous dose of Tecvayli® should be instructed to remain within proximity of a healthcare facility and monitored for signs and symptoms daily for 48 hours.For ICANS and other neurologic toxicities, treatment with Tecvayli® should be withheld as indicated (see product information).

- 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 product information).
- Management of neurologic toxicities
  - At the first sign of neurologic toxicity, including ICANS, neurology evaluation should be considered. Other causes of neurologic symptoms should be ruled out. Tecvayli® should be withheld until adverse reaction resolves (see product information). Intensive care and supportive therapy should be provided for severe or life-threatening neurologic toxicities. General management for neurologic toxicity (e.g., ICANS with or without concurrent CRS) is summarised in product information.

❖ Infections
- Severe, life-threatening, or fatal infections have been reported in patients receiving Tecvayli® (see product information). New or reactivated viral infections occurred during therapy with Tecvayli®. Progressive multifocal leukoencephalopathy has also occurred during therapy with Tecvayli®.
- Patients should be monitored for signs and symptoms of infection prior to and during treatment with Tecvayli® and treated 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. For subsequent doses, Tecvayli® should be withheld as indicated (see product information).

❖ Hepatitis B virus reactivation
- Hepatitis B virus reactivation can occur in patients treated with medicinal products 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 Tecvayli® treatment.
- In patients who develop reactivation of HBV while on Tecvayli®, treatment with Tecvayli®should be withheld as indicated in product information and manage per local institutional guidelines (see product information).

❖ Hypogammaglobulinaemia
- Hypogammaglobulinaemia has been reported in patients receiving Tecvayli® (see product information).
- Immunoglobulin levels should be monitored during treatment with Tecvayli®. Intravenous or subcutaneous immunoglobulin therapy was used to treat hypogammaglobulinemia in 39% of patients. Patients should be treated according to local institutional guidelines, including infection precautions, antibiotic or antiviral prophylaxis, and administration of immunoglobulin replacement.

❖ Vaccines
- Immune response to vaccines may be reduced when taking Tecvayli®. The safety of immunisation 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 least 4 weeks after treatment.

❖ Neutropenia
- Neutropenia and febrile neutropenia have been reported in patients who received Tecvayli® (see product information).
- Complete blood cell counts should be monitored at baseline and periodically during treatment. Supportive care should be provided per local institutional guidelines.
- Patients with neutropenia should be monitored for signs of infection. Treatment with Tecvayli® should be withheld as indicated (see product information).

❖ Excipients
- This medicinal product contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially 'sodium-free'.

Costs

3 ml Tecvayli® solution for injection 10 mg/ml = € 905.00 (ex-factory price) [8]

Study characteristics [4, 9-12]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
MajesTEC-1 NCT03145181 and NCT04557098	165	weekly subcutaneous injection of teclistamab (at a dose of	-	overall response (partial response or better)	ongoing[3], multicentre, open label, single-arm, phase 1/2 clinical trial	-	Janssen Research and Development	[4]

[3] NCT04557098 is ongoing until 12/2014; NCT03145181 is ongoing until 01/2025.

		1.5 mg per kg of body weight) after step-up doses of 0.06 mg and 0.3 mg per kg						

Efficacy; results from the pivotal phase 1–2 portion of MajesTEC-1	**Safety;** results from the pivotal phase 1–2 portion of MajesTEC-1
Median follow-up: 14.1 months (range, 0.3-24.4) **Overall response rate:** 63.0% (95% CI, 55.2-70.4) **Very good partial response or better:** 58.8% **Complete response or better**: 39.4% **Median time until the first response:** 1.2 months (range, 0.2-5.5) **Median time until a best response:** 3.8 months (range, 1.1-16.8) **Negativity for minimal residual disease (at a threshold of 10–5):** 26.7% (95% CI, 20.1-34.1) **Among the 65 patients who had a complete response or better, 46% had no minimal residual disease.** **Median duration of response:** 18.4 months (95% CI, 14.9-not estimable); not yet mature **Kaplan–Meier estimate of maintenance of response for at least 12 months:** 68.5% (95% CI, 57.7-77.1) **Median duration of PFS:** 11.3 months (95% CI, 8.8-17.1) **Median duration of OS:** 18.3 months (95% CI, 15.1-not estimable); not mature after censoring of data for 97 patients <u>Pharmacokinetics, Immunogenicity, and Biomarkers</u> ❖ Teclistamab exposure was sustained over the predetermined target level (6 µg per milliliter, based on the upper boundary of an experimentally determined range of the 90% maximal effective concentration) with a low peak-to-trough ratio. ❖ Of the 146 patients who had received the recommended phase 2 dose and could be evaluated for immunogenicity, none were found to have antibodies against teclistamab. ❖ Serum levels of soluble BCMA were assessed as a potential marker of tumour burden and response. ❖ 13 rapid decreases in total levels of soluble BCMA occurred in 40 of 59 evaluable patients (68%) who had a partial response or better within the first month of treatment. ❖ Increased soluble BCMA levels occurred in 27 of 28 patients (96%) who did not have a response to teclistamab during cycle 1. ❖ Reductions in soluble BCMA levels occurred during the first 4 cycles of treatment in 63 of 72 evaluable patients (88%) who had a partial response or better, whereas all the evaluable patients who did not have a response (9 of 9 patients) had increased levels of soluble BCMA. ❖ Reductions in soluble BCMA levels were greater in patients with a deeper response. ❖ Pharmacodynamic induction of cytokines and T-cell activation were observed after the administration of teclistamab. No significant associations were observed between treatment response and maximum change in cytokine levels or T-cell activation; patients who had response to treatment had higher levels of interferon-γ, interleukin-6, interleukin-10, and interleukin-2 receptor α than those without a response; they also had higher cell-surface levels of CD38 or T-cell	**AEs grade 3 or 4:** n=156/165 (94.5%) **Discontinued of teclistamab due to AEs:** n=2 (grade 3 adenoviral pneumonia and grade 4 progressive multifocal leukoencephalopathy) **Infections grade 3 or 4:** n=74/165 (44.8%) **Cytokine release syndrome:** n=119/165 (72.1%) **Investigator-assessed neurotoxic events (including immune effector cell–associated neurotoxicity syndrome):** n=24/165 (14.5%) **Deaths:** n=68/165 (41.2%)[4] **Deaths considered by investigators to be related to teclistamab:** n=5[5]

[4] Most deaths (n=41) were attributed to progressive disease. 19 patients died from AEs, including 12 deaths from Covid-19.

[5] In 1 patient who had discontinued teclistamab due to progressive multifocal leukoencephalopathy, in 2 patients who had contracted Covid-19, in 1 patient who had hepatic failure, and in 1 patient who had streptococcal pneumonia.

immunoglobulin and mucin domain–containing protein 3 on CD8+ T cells, which suggests that immune activation that occurred early after treatment initiation may be a predictor of clinical response.	

ESMO-MCBS version 1.1 [13, 14][6]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	3	-	ORR: 63.0%	-	ORR (PR+CR) ≥ 60%	3	-	-	-	3

Risk of bias - study level (case series) [15]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	partial	yes	yes	yes	no
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	unclear	yes	yes	unclear	yes
Overall risk of bias: moderate								

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Abbreviations: AE=adverse event, AJ=adjustment, BCMA=B-cell maturation antigen, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CRS=cytokine release syndrome, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HBV=Hepatitis B virus, HR=hazard ratio, I=intervention, ICANS= Immune Effector Cell-Associated Neurotoxicity Syndrome, Int.=intention, MG=median gain, MM=multiple myeloma, n=number of patients, NICE=National Institute for Health and Care Excellence, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment

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[6] **Disclaimer**: Though not finally validated, but feasibility tested in [14], the original ESMO MCBS v1.1. was found to be widely applicable also for haematological malignancies. Hence, from October 2022, ESMO assessments were also carried out for haematological indications in new fact sheets and updates.

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