swissmedic

Date: 11 April 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Tecvayli

International non-proprietary name: teclistamab

Pharmaceutical form: solution for injection

Dosage strength(s): 153 mg/1.7 ml, 30 mg/3 ml

Route(s) of administration: subcutaneous

Marketing authorisation holder: Janssen-Cilag AG

Marketing authorisation no.: 68747

Decision and decision date: temporary authorisation in accordance with Art. 9a TPA on 22 December 2022

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADC	antibody drug conjugate
AE	Adverse event
AKI	Acute kidney injury
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BCMA	B-cell maturation antigen
CAR T-cells	Chimeric antigen receptor T-cells
cBCMA	cynomolgus monkey B-cell maturation antigen
CD3	Cluster of differentiation 3
CHO	Chinese hamster ovary
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CR	Complete response
CRS	Cytokine release syndrome
DCO	data cut-off
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group (performance status)
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
hBCMA	human B-cell maturation antigen
HC	Heavy chain
ICANS	immune effector cell-associated neurotoxicity syndrome
ICH	International Council for Harmonisation
IFN-γ	Interferon gamma
IgG4	Immunoglobulin G4
IL-8	Interleukin 8
IMiD	Immunomodulatory imide drug
IMWG	International Myeloma Working Group
IRC	Independent review committee
ISS	International staging system
LC	Light chain
MAH	Marketing Authorisation Holder
Max	Maximum
MM	Multiple myeloma
MRD	Minimal residual disease
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PD	progressive disease
PD1	Programmed cell death receptor-1
PD-L1	Programmed cell death receptor-1 ligand-1
PFS	Progression-free survival
PI	Proteasome inhibitor
PK	Pharmacokinetics
PML	Progressive multifocal leukoencephalopathy
PopPK	Population pharmacokinetics
PR	Partial response
RP2D	Recommended Phase 2 dose
RMP	Risk management plan
RRMM	Relapsed or refractory multiple myeloma

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SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TNF-α	Tumour necrosis factor alpha
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TTR	Time to response

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New active substance status
The applicant requested new active substance status for teclistamab in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 22 March 2023.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Article 9a TPA.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is a programme for the assessment of promising cancer treatments coordinated by the FDA. It provides a framework for concurrent submission and review of oncology products among international partners.

2.2 Indication and dosage

2.2.1 Requested indication

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.

2.2.2 Approved indication

TECVAYLI as monotherapy is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, and have demonstrated disease progression to the last line of therapy (see Properties/Effects).

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended doses of teclistamab are administered subcutaneously and based on actual body weight.
Step-up Dosing Schedule:
•Step-up Dose 1: 0.06 mg/kg first day of treatment
•Step-up Dose 2: 0.3 mg/kg, two to four days after Step-up Dose 1
•Treatment Dose: 1.5 mg/kg, two to four days after Step-up Dose 2

Teclistamab should be administered according to the step-up dosing schedule listed above to reduce the incidence and severity of CRS. The recommended dosage of teclistamab is 1.5 mg/kg actual body weight administered once weekly after completion of the step-up dosing schedule. Teclistamab should be continued until disease progression or unacceptable toxicity.

2.2.4 Approved dosage

(see appendix)

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2.3 Regulatory history (milestones)

Application	27 January 2022
Formal control completed	15 February 2022
Preliminary decision	23 August 2022
Response to preliminary decision	14 October 2022
Final decision	22 December 2022
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical context

Multiple myeloma (MM) is a plasma cell neoplasm that accounts for approximately 1 to 2% of all cancers and is the second most common haematological malignancy, with an estimated incidence in Europe of approximately 5 to 6/100,000/year. The incidence increases with age, and the median age at onset of MM is approximately 70 years, with approximately two thirds of patients aged older than 65 years. Although survival from the time of diagnosis of MM has improved since 2000, the prognosis of patients with relapsed or refractory MM (RRMM) following prior exposure to all three MM drug classes is poor, and the remaining therapeutic options are limited (Dimopoulos et al. 2021; Cowan et al. 2022). Most of these patients have triple-class refractory disease, and many have been exposed to all five drugs that have demonstrated single-agent effectiveness: bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab (so-called penta-exposed patients). Historically, this patient population achieved objective response rates (ORR) of approximately 30%, median progression-free survival (PFS) of approximately 3 to 6 months, and median overall survival (OS) of approximately 6 to 12 months (Gandhi et al. 2019).

With the present application, Tecvayli has been proposed for the treatment of RRMM following prior exposure to all three MM drug classes, based on the results of Study MajesTEC-1 (64007957MMY1001). Study MajesTEC-1 was a single-arm, open-label, multicentre Phase 1/2 study of Tecvayli administered as monotherapy to adult patients with triple-class exposed RRMM who had received at least 3 prior lines of systemic therapy. While the Phase 1 part focused on dose escalation and selection of the recommended Phase 2 dose (RP2D), the pivotal Phase 2 part focused on investigating the efficacy and safety of Tecvayli in the proposed patient population.

References

- Dimopoulos MA et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2021;32:309-322 (including corrigendum 2022: https://doi.org/10.1016/j.annonc.2021.10.001).
- Cowan AJ et al. Diagnosis and Management of Multiple Myeloma – A Review. JAMA 2022;327:464-477.
- Gandhi UH et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia 2019;33:2266–2275.

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4 Quality aspects

4.1 Drug substance

Teclistamab drug substance is a humanised immunoglobulin G4 (IgG4) bispecific antibody against B-cell maturation antigen (BCMA) and cluster of differentiation 3 (CD3) receptors, with a molecular mass of 146,261 Da for the predominant glycoform. Teclistamab is a heterodimer consisting of two different heavy chains (HC) and two different light chains (LC), joined by disulfide bonds. Amino acid substitutions in the CH3 domain of one parental antibody's HC enable preferential refolding of the heterodimer. Teclistamab utilises an IgG4 proline-alanine-alanine scaffold that stabilises the hinge region and suppresses FcγR binding. 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.
The parental monospecific monoclonal antibodies, anti-BCMA and anti-CD3 are each produced separately by mammalian Chinese hamster ovary (CHO) cell lines.
The generation, characterisation and control of the host cell lines, and the establishment of the recombinant master and working cell banks used for production of anti-BCMA and anti-CD3 parental antibodies are described in sufficient detail.
The upstream manufacturing process of both parental antibodies uses suspension cells and serum-free media. The parental antibodies are secreted into the culture medium and separated from cell debris by filtration steps followed by chromatographic purification. Formation of the bispecific teclistamab is conducted through reduction and oxidation of the parental monospecific monoclonal antibodies. The purification process comprises several chromatographic and filtration steps as well as virus inactivation and virus retention filtration.
The manufacturing process of teclistamab is validated with several consecutive batches, and the data demonstrated a consistent production and an efficient removal of impurities.
The specifications for drug substance release and stability include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, and potency. Specifications are based on clinical experience, batch analysis data, stability data, and are in conformance with current compendial or regulatory guidelines. All specific analytical methods are described in sufficient detail and are fully validated.
Teclistamab drug substance is stored frozen. The established shelf life of the drug substance is justified by the results of ICH-conform stability studies.

4.2 Drug product

The teclistamab drug product is supplied as a sterile liquid in a vial presentation for subcutaneous administration. Two different presentations are available, one containing 90 mg/ml teclistamab and the other containing 10 mg/ml teclistamab, and the 10 mg/ml presentation is intended for the step-up dosing regimen only.
Each 10 mg/mL drug product vial contains 30 mg of teclistamab in a 3.0 mL nominal fill volume, and each 90 mg/mL teclistamab drug product vial contains 153 mg of teclistamab in a 1.7 mL nominal fill volume. Both presentations are for single-use only and are preservative-free. The formulation is an aqueous buffered solution of pH 5.2 containing an acetic buffer, EDTA, sucrose, and polysorbate 20. All excipients comply with the European Pharmacopoeia.
The manufacturing process of the finished drug product consists of thawing, compounding and dilution steps, sterile filtration, aseptic filling/stoppering/sealing, inspection, labelling and secondary packaging. Process validation studies were conducted at the commercial scale.
The manufacturing process of drug substance and drug product include adequate control measures to prevent contamination and maintain control with regard to adventitious agents safety.
The release and stability specifications were established as part of an integrated control strategy and are derived from compendial guidelines, product and process knowledge, and statistical analysis of 10 and 90 mg/mL DP release and stability data. They include relevant tests and limits, e.g. for identity, appearance, colour of solution, pH, turbidity, osmolality, purity and impurities tests, potency assay, protein concentration, extractable volume, particulate matter, sterility, container closure

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integrity and bacterial endotoxins. All non-compendial methods are fully validated in accordance with current regulatory guidance.
The drug product is stored at 2 – 8°C protected from light. The claimed shelf life of 18 months is justified based on ICH-conform stability studies. Compatibility studies of drug product with syringes made of polycarbonate and polypropylene demonstrated that the physical and biochemical integrity was retained for up to 20 hours at 2-8°C or at room temperature.

4.3 Quality conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical aspects

A limited nonclinical programme was conducted for teclistamab, in line with ICH S6(R1) and ICH S9.

5.1 Pharmacology

In vitro biochemical studies demonstrated teclistamab binding to human B-cell maturation antigen (hBCMA) and cynomolgus monkey BCMA (cBCMA) with dissociation constants (Kds) of 0.18 and 6.5 nM. Teclistamab bound cBCMA-expressing CHO cells with an EC_{50} of 23 nM, hBCMA+ multiple myeloma (MM) cell lines with EC_{50s} in the low nanomolar range, and primary bone marrow mononuclear cells from MM patients. Kds for CD3 binding were similar for human and for cynomolgus monkey T cells (28 nM and 38 nM respectively). Teclistamab had a 2- to 20-fold higher potency for hBCMA- than for cBCMA-mediated killing of CHO cells in the presence of human T cells. Teclistamab showed potent T cell-mediated activity against hBCMA+ MM cell lines, bone marrow mononuclear cells from MM patients, and in whole blood of normal donors spiked with an MM cell line with EC_{50} values in the lower nanomolar range.
Binding and sequence alignment data did not suggest any activity on BCMA and/or CD3 of rodents or rabbits.
Studies with proliferation-inducing ligand (APRIL) and B-cell activating factor (BAFF), known ligands of BCMA, and soluble BCMA (sBCMA), did not suggest any clinically relevant interference with teclistamab activity. In contrast, teclistamab may interfere with BAFF- and APRIL-mediated BCMA signalling.
In a tumour model in NSG mice, teclistamab inhibited tumour growth ≥79% at intraperitoneal doses ≥0.5 mg/kg.

Secondary pharmacodynamic studies were not conducted, which is considered acceptable. Tissue cross-reactivity studies with cynomolgus monkey and human tissues did not indicate any binding to reproductive organs or cardiac, lung, brain, peripheral nerve, or spinal cord tissues. Teclistamab, as an IgG4 with a modified Fc region and reduced Fcγ receptor binding, is expected to have a reduced Fc effector function. Therefore, no functional studies were conducted, which is acceptable.

Cardiovascular, respiratory, and central nervous system function was assessed in the pivotal cynomolgus monkey 5-week repeat-dose toxicity study, in line with ICH S6(R1). No effects were noted at the highest administered dose.

5.2 Pharmacokinetics

Analytical methods were appropriately validated for the detection of teclistamab and ADAs in cynomolgus monkey blood.
Pharmacokinetic and toxicokinetic profiles were evaluated in two toxicology studies conducted in cynomolgus monkeys. After single and repeated dosing, C_{max} and AUC_{last} increased approximately dose-proportionally over the dose range of 0.1-30 mg/kg/day. There were no gender differences in exposure, and no accumulation > 2-fold occurred after repeated dosing.
Traditional distribution, metabolism, excretion, and drug interaction studies were not performed, in line with ICH recommendations. ADAs were detected in the majority of animals in the pivotal 5-week toxicology study. Exposure was decreased in only 7 out of 21 ADA-positive animals. However, the possibility that residual teclistamab interfered with ADA detection could not be excluded but, overall, the validity of the study was not considered to be affected by ADAs. Immunogenicity in clinical studies was low (≤ 0.5% patients with neutralising antibodies).

5.3 Toxicology

The cynomolgus monkey was selected for the toxicology studies based on the protein sequence homology of > 90% for cBCMA and hBMCA and on demonstrated pharmacological activity. The

clinical weekly dosing scheme was used. Doses were administered intravenously (IV) in contrast to the clinical subcutaneous (SC) route, as this was the initially planned clinical administration route. Exposures upon IV administration are expected to be similar to, or exceed, exposures after SC administration, and the divergent administration routes are not considered to affect the validity of the toxicology study. A non-GLP study with single doses of 0.1, 1, and 10 mg/kg and a pivotal study with weekly doses of 1, 10, and 30 mg/kg for 5 weeks did not show any teclistamab-related effects. Although all doses resulted in exposures above the pharmacological effective *in vitro* concentration for cytotoxicity, no pharmacological effects were noted. This is probably due to the lower binding affinity to cBMCA compared to hBCMA, and the lower BCMA target expression in cynomolgus monkey compared to MM patients. Binding of teclistamab to CD3 was shown by immunohistochemistry and flow cytometry, which however did not result in T cell activation or changes in the number of immune cells or cytokine levels. The highest dose level of 30 mg/kg was considered the NOEL, associated with exposures 43-fold C_{max} and 22-fold AUC_{tau} at human steady-state exposure at 1.5 mg/kg. Considering the ~36-fold lower affinity of teclistamab to cBCMA compared to hBCMA, the toxicology study and the exposure multiples are not considered to inform appropriately on safety in patients. The lack of effects in healthy monkeys is in contrast to the strong pharmacology-related adverse effects in humans (*e.g.,* cytokine release syndrome associated with cardiovascular and central nervous system effects, hypogammaglobulinaemia, neutropenia and increased infection risk).
Genotoxicity, carcinogenicity, and reproductive and development toxicology studies were not conducted, in line with ICH S6(R1) recommendations. As teclistamab induces T cell activation and cytokine release, pregnancy may be adversely affected. Appropriate recommendations for contraception, pregnancy, and breast-feeding are included in the information for healthcare professionals.

A local tolerance study in rabbits with SC administration showed slight erythema at the injection site, a common site reaction in humans.
Teclistamab was not haemolytic and did not induce serum coagulation or precipitation in blood of normal donors. In whole blood from normal donors, teclistamab induced low levels of TNF-α at ≥ 3 ng/mL, and of IL-8 and IFN-ɣ at ≥ 82 ng/mL in a dose-dependent manner. Cytokine release syndrome is a common adverse effect in patients, and appropriate measures are recommended in the information for healthcare professionals.
Teclistamab is indicated only for adults. Juvenile studies are not required.
There are no concerns with regard to the excipients or impurities.
An environmental risk from an antibody such as teclistamab is not expected.
The RMP appropriately summarises the nonclinical data for teclistamab and the risks associated with the class of T cell engagers.

5.4 Nonclinical conclusions

Overall, the pharmacological properties of teclistamab were sufficiently characterised in nonclinical studies. The toxicology study including safety pharmacology endpoints conducted in the cynomolgus monkey did not show any biological or associated toxicological effects. Effective exposure levels were similar to the clinical exposure, which is considered acceptable for the requested indication.

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6 Clinical and clinical pharmacology aspects

6.1 Clinical pharmacology

Bioanalytics: Validated bioanalytical assays were used for the determination of teclistamab serum concentrations and for the assessment of immunogenicity (presence of ADAs and neutralising antibodies).

Biopharmaceutics: The drug product intended for the market was used in the clinical study.

Pharmacokinetics: The pertinent pharmacokinetic (PK) / pharmacodynamic information in support of this application was derived from the MajesTEC-1 study. For PK and immunogenicity data, the data cutoff was 09 August 2021.

The available PK data were analysed in a popPK analysis. A two-compartment model with parallel time-independent and time-dependent clearance pathways was selected as the final population pharmacokinetic model, which best described the observed teclistamab concentration data. The time-independent clearance component is thought to reflect the endogenous catabolic processes of IgG degradation. The time-dependent clearance component corresponds to the decrease in drug clearance as disease status improves over time, which is thought to be related to tumour burden or target amount. None of the factors investigated in the popPK analysis (i.e. age, sex, body weight, race, region, ethnicity, creatinine clearance, albumin concentration, renal impairment [mild, moderate or severe], hepatic impairment [mild], baseline soluble BCMA, bone marrow percent plasma cells, plasmacytoma, ECOG status, ISS/revised ISS stage, type of myeloma [IgG vs non-IgG], number of prior lines of therapy, prior use of daratumumab, prior use of anti-PD1/anti-PDL1, prior use of anti BCMA treatment, refractory status, immune response status, and drug product) was identified as having a meaningful effect on teclistamab pharmacokinetic behaviour.

Based on the final popPK model, the volumes of distribution were 4.09 Lfor the central compartment and 1.29 l for the peripheral compartment. The time-independent clearance was 0.545 l/day. According to non-compartmental analyses, the average half-life of elimination following intravenous administration was 3.8 days.

No dedicated studies in patients with renal and hepatic impairment were conducted. The popPK analysis suggested the absence of a meaningful impact of mild hepatic impairment and of mild and moderate renal impairment on teclistamab.

The final population pharmacokinetic model was used to simulate concentration-time profiles following the RP2D (1.5 mg/kg teclistamab SC administered weekly, with the first treatment dose preceded by step-up doses of 0.06 mg/kg and 0.3 mg/kg). Steady state levels were attained in Cycle 3 (the 7th treatment dose; Day 43) following the proposed dosing regimen. Mean accumulation ratios following multiple 1.5 mg/kg SC weekly doses was 2.71- and 3.05-fold for C_{max} and AUC_{tau}, respectively. Based on available AUC_{tau} values at steady state from all IV and SC weekly dosing cohorts, mean bioavailability following SC weekly administration for the treatment dose was 69%.

Immunogenicity: The teclistamab-mediated immunogenicity potential was low. None of the patients treated with the recommended Tecvayli dosing developed antibodies against teclistamab.

6.2 Dose finding and dose recommendation

The registrational treatment dose of Tecvayli monotherapy (1.5 mg/kg SC administered weekly, with the first treatment dose preceded by two step-up doses of 0.06 and 0.3 mg/kg) was selected based on the pharmacokinetic, pharmacodynamic, safety, and efficacy data available from the Phase 1 dose escalation part of the pivotal Study MajesTEC-1. This dosage corresponds to the RP2D used in all patients of the pivotal Phase 2 part of Study MajesTEC-1.

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The available evidence suggests that efficacy in terms of ORR and time-to-event endpoints, such as duration of response (DOR), PFS and OS, might be comparable at RP2D and lower dosages, e.g. if Phase 1 results of the RP2D cohort (N=40) and 0.72 mg/kg subcutaneous (SC) weekly cohort (N=15) are compared. However, the number of patients and the range of concentrations studied at non-RP2D dosages are too low and the time-to-event endpoint is too immature to draw valid conclusions. Even though a positive exposure-efficacy relationship was reported in the 72 Phase 1 SC subjects (28 at <RP2D, 40 at RP2D, and 4 at >RP2D), this might have been biased by lumping the 15 patients on 0.72 mg/kg SC weekly together with lower dosages into the <RP2D cohort. Similarly, although safety does not appear to differ across investigated dosages, the number of patients and the range of concentrations studied at lower dosages are too low to confirm less toxicity when Tecvayli dosage is reduced. This uncertainty is of particular relevance as approximately two-thirds of patients treated with Tecvayli SC at RP2D experienced at least one treatment-emergent adverse event (TEAE) leading to cycle delay or dose interruption, and substantial proportions of patients reported TEAEs, including neurological TEAEs and cytokine release syndrome (CRS). Moreover, it is noted that the use of lower step-up doses of Tecvayli had been implemented to mitigate the risk of CRS.

Another relevant aspect regarding dose finding is that patients of the pivotal Study MajesTEC-1 could reduce dosing frequency from weekly dosing in case of response. The results of the requested additional analyses suggest that extending the dosing interval to every-2-week dosing (Q2W) after achieving the specified responses – PR or better over at least 4 cycles in Phase 1, CR or better for at least 6 months in Phase 2 – may not negatively affect efficacy in terms of DOR, PFS, and OS. In many instances, the efficacy results were even numerically better in patients who had their dosing interval extended to Q2W, especially in Phase 1 patients treated with R2PD. However, as assignments were not randomised and patient numbers were small, data need to be interpreted cautiously. Still, predicted median trough levels after Q2W dosing are expected to be higher than the maximum EC90 value, which had been defined as the minimum trough level of Tecvayli to achieve efficacy.

Following Swissmedic's request, the limited evidence and uncertainties regarding dose finding and selection have been adequately reflected in the information for healthcare professionals.

6.3 Efficacy

The pivotal Phase 2 part of Study MajesTEC-1 was comprised of two cohorts of patients with triple-class exposed RRMM who had received at least 3 prior lines of systemic therapy. While Cohort A excluded prior treatment with any BCMA-targeted therapy, Cohort C was to include only patients who had also received an anti-BCMA treatment with CAR-T cells or an ADC and was designed to investigate whether patients with RRMM that progressed on prior BCMA-directed therapy (CAR T-cells or ADC) could respond to subsequent BCMA-directed therapy with Tecvayli.

Several eligibility restrictions have been considered not representative for the targeted population, which is comprised of a heavily pre-treated elderly population in a very advanced disease stage and with significant comorbidities. This regards the exclusionary limits used for hypercalcaemia, renal insufficiency, and anaemia as well as the limitation to performance status of ECOG 0 and 1 – see information for healthcare professionals.

The study drug was to be administered to subjects until disease progression or unacceptable toxicity. All subjects were to receive premedication prior to each step-up dose and the first treatment dose of Tecvayli, including steroids, antihistamines, and antipyretics. Additionally, subjects who experienced Grade ≥2 CRS or systemic administration-related reactions (sARRs) were required to receive dexamethasone prior to the next dose of Tecvayli, and subjects who experienced any grade CRS or sARRs were required to receive the antihistamine and antipyretic prior to at least the next dose of Tecvayli. Dose delay was the primary method for managing toxicities related to Tecvayli, and no patients treated at pivotal RP2D underwent dose reduction.

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Disease evaluations were to be performed at screening and prior to study drug administration at each cycle (28-day in Phase 2), using a central laboratory. Radiographic assessments of disease status were to occur every 12 weeks. During treatment, and before disease progression was confirmed, x-rays or CT scans were to be performed locally, whenever clinically indicated based on symptoms, to document progression. Bone marrow samples to assess for plasma cell percentage and clonality were to be analysed locally; bone marrow samples to assess for minimal residual disease (MRD) negativity were to be analysed centrally. Disease evaluations were to be continued until disease progression, even after discontinuation of study therapy.

An Independent Review Committee (IRC) was to perform an independent review of data from participants treated at the RP2D with Tecvayli and provide an independent determination of response / progressive disease (PD) based on the 2016 international myeloma working group (IMWG) consensus criteria in combination with clinical judgement.

In the pivotal Phase 2 part of Study MajesTEC-1, the primary objective was to evaluate efficacy of Tecvayli at the RP2D, with IRC-assessed ORR as the primary endpoint.

There were multiple secondary efficacy endpoints including DOR, time to response (TTR), PFS, OS, and MRD-negativity rate. Given the absence of a control arm, sample size calculations and type I error control, these endpoints have been considered exploratory.

All treated Phase 2 patients from both Cohort A and Cohort C (N=125 and 38, respectively) have been considered the primary population for efficacy (in total N=163), while Phase 1 data were supportive only. The Swissmedic Clinical Assessment has focused on the primary analysis that was based on the pre-specified primary data cut-off (DCO) 07 September 2021. However, because time-to-event endpoints such as DOR, PFS and OS were immature at this time point, the focus for their assessment has been on the subsequently submitted data from the latest DCO 16 March 2022.

As of DCO 07 September 2021, approximately 40% of Phase 2 Cohort A and Cohort C patients had discontinued the study drug, most commonly due to progressive disease (23% and 29%, respectively) followed by death (7% and 10.5%, respectively). Approximately 26% and 18% of Phase 2 Cohort A and Cohort C patients, respectively, had discontinued study participation, most commonly due to death (23% and 18%, respectively).

Duration of exposure to Tecvayli and follow-up were short in the primary efficacy population (N=163). These patients had a median duration of exposure to Tecvayli of less than 6 months, with only 38% (62/163 patients) exposed to Tecvayli for 6 months or longer, while median duration of follow-up did not exceed 6.5 months at DCO 07 September 2021. Data updates increased the median duration of exposure and follow-up to approximately 7.5 months and 1 year, respectively, which is still short and was associated with insufficiently mature time-to-event endpoints such as OS.

The median age of Phase 2 Cohort A and Cohort C patients was 64 years with, in total, 13% (15% and 5%, respectively) being at least 75 years of age, which is younger than one would expect from an MM population. The majority of Phase 2 patients were male (in total 58%; 56% and 63%, respectively), White (in total 82%; 80% and 90%, respectively), and performance status was approximately 70% ECOG 1 vs. 30% ECOG 0.

IgG was the most common immunoglobulin isotype in approximately 56% of Phase 2 patients (59% and 47% of Cohort A and Cohort C patients, respectively, followed by light chain MM in approximately 24% (20% and 37%, respectively). The median time from diagnosis of multiple myeloma to 1st study dose was 6.2 years (range: 0.8 to 23) and 6.5 years (range: 1.1 to 24), respectively.

Extramedullary plasmacytoma at baseline was present in 19% of Phase 2 patients (16% and 29% of Cohort A and Cohort C patients, respectively), and approximately 12% had 60% or more plasma cells in the bone marrow (biopsy or aspirate). High-risk cytogenetics was present in 26% (24% and 32%, respectively), most frequently del(17p) and t(4;14). Revised ISS (R-ISS) staging was Stage I in 22% (23.5% vs. 16%, respectively), Stage II in approximately 70%, respectively, and Stage III in 10% (8% vs. 13.5%, respectively).

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Almost all the treated Phase 2 Cohort A and Cohort C patients (161 out of 163) had received at least 3 prior lines of MM therapy; the median number of lines of prior therapy was 5 (range: 2 to 14) overall, and 5 (range: 2 to 14) in Cohort A and 6 (range: 3 to 14) in Cohort C, respectively. All 163 Phase 2 patients (100%) were triple-class exposed (proteasome inhibitor (PI), immunomodulatory imide drug (IMiDs), and anti-CD38 monoclonal antibody), and a majority, overall 74% (72% and 79%, respectively), were penta-exposed (at least 2 PIs, at least 2 IMiDs, and at least 1 anti-CD38 monoclonal antibody). In addition, all patients in Cohort C had received prior anti-BCMA therapy, approximately 70% ADC and 40% CAR T-cells. Triple-class refractoriness was reported for 79% of Phase 2 patients (77% and 84% of Cohort A and Cohort C patients, respectively), and penta-refractoriness for 28% (27% and 32%, respectively). In addition, approximately two thirds of patients in Cohort C were reportedly refractory to any anti-BCMA therapy, 58% to ADC and 13% to CAR T-cells. Overall, 90% of all Phase 2 patients were classified as refractory to last line therapy (92% and 84%, respectively).

Subsequent anti-myeloma therapy was allowed at the discretion of the investigator after disease progression was established per the IMWG criteria. Overall, 22% of Phase 2 patients received subsequent systemic anti-myeloma therapy or radiotherapy (21% and 26% in Cohort A and Cohort C, respectively). The most frequent therapies were glucocorticoids (overall 15%; 13% and 21%, respectively), nitrogen mustard analogues (approximately 10% in both cohorts), mostly cyclophosphamide, proteasome inhibitors (overall 10%: 8% and 18%, respectively), and anthracyclines (overall 4%; 2% and 11%, respectively), mostly doxorubicin.

Primary endpoint

The best IRC-assessed ORR (partial response (PR) or better) in the pooled Phase 2 population of Cohort A and Cohort C (N=163) was 57% (95%CI 49, 65) using IMWG 2016 criteria based on data from DCO 07 September 2021, with 20% achieving responses of CR or better (stringent CR + CR). In Cohort A (N=125), the best IRC-assessed ORR was 62% (95%CI 53, 70), with 21% achieving responses of CR or better. In Cohort C (N=38), the best IRC-assessed ORR was 42% (95%CI 26, 59), with 18% achieving responses of CR or better.

Results of sensitivity analyses for ORR were consistent with the primary analysis for Cohort A and Cohort C.

Secondary endpoints

Duration of response (DOR)

Based on an update as of DCO 16 March 2022, the event rate among the 98 responders in the pooled Phase 2 population (N=163) of Cohort A (78 responders) and Cohort C (20 responders) was 30% (31% and 25% in Cohort A and Cohort C, respectively). Estimated median DOR was 14.9 months (95% CI 14,9, not estimable) in the pooled Phase 2 population and in Cohort A, while it was not estimable in Cohort C (lower limit of 95% CI 10.5 months). The probability of responders to remain in response at 6 months was approximately 87% (90% and 79%, respectively) and, at 12 months, approximately 66% (67% and 64%, respectively).

Progression-free survival (PFS)

Based on an update as of DCO 16 March 2022, maturity in the pooled Phase 2 population (N=163) was 53% (51% and 61% in Cohort A and Cohort C, respectively). Estimated median PFS was approximately 10 months, but differed between cohorts and was shorter in Cohort C (10.5 months vs. 4.5 months). PFS at 12 months was 43%, and again differed between both cohorts and was lower in Cohort C (46% vs. 32%).

Overall survival (OS)

Based on an update as of DCO 16 March 2022, overall maturity in the pooled Phase 2 population and the individual Phase 2 cohorts was 42%. Estimated median OS was 16 months in the pooled Phase 2 population, and was similar in Cohort A and Cohort C (16 and 14.4 months, respectively). OS at 12 months was approximately 60%, and again similar in both cohorts (60% and 59%, respectively).

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Minimal Residual Disease (MRD) negativity

Approximately 12% / 20% of patients with PR / CR or better had no bone marrow samples for MRD evaluation. In addition, in those who had bone marrow samples, calibration failed in approximately 30%. Thus, MRD results are not robust.

6.4 Safety

The focus of the following safety assessment has focused on the subsequently submitted data from the latest DCO 16 March 2022. As of this DCO, all patients treated at RP2D (RP2D/Cohort C; N=203) and all patients treated in the MajesTEC-1 study (Total MajesTEC-1; N=340) reported at least one TEAE, which were judged as drug-related in up to 94% of these patients. The most frequently reported AEs were:

- Blood and lymphatic system disorders in approximately 90% of patients, mainly cytopenias, including neutropenia (65-70%), anaemia (50-55%), thrombocytopenia (40%), lymphopenia (30-35%), and leukopenia (15-20%).
- General disorders and administration site conditions in 75-80% of patients, including pyrexia (30%), fatigue (25%) and, after SC administration, injection site erythema (20-30%).
- Infections and infestations in 75% of patients, mainly pneumonia (15%), COVID-19 (15%), and upper respiratory tract infection (10-15%). Opportunistic infections were reported in 10% of patients treated at RP2D, Pneumocystis jirovecii pneumonia being the most common (3%); of note, one fatal case of progressive multifocal leukoencephalopathy (PML) was reported.
- Immune system disorders in 70-75% of patients, mainly due to CRS (up to 71%); hypogammaglobulinaemia (15%).
- Musculoskeletal and connective tissue disorders in 60-65% of patients, including arthralgia (25%), back pain (15-20%), bone pain (15-20%), and pain in extremity (15%).
- Gastrointestinal disorders in 60-65% of patients, including diarrhoea (30%), nausea (25%), constipation (20-25%), and vomiting (10-15%).
- Metabolism and nutrition disorders in 55% of patients, including decreased electrolytes (potassium, phosphorus, calcium, magnesium) and decreased appetite in 10-15%.
- Respiratory, thoracic and mediastinal disorders in 50% of patients, including cough (20%) and dyspnoea (10-15%).
- Nervous system disorders in 45-50% of patients, mainly headache (25%).
- Investigations in 35-40% of patients, including increased liver function tests (ALT, AST, gamma-GT) in 10%.
- Vascular disorders in 30% of patients, including hypertension in 10%.

Grade 3 / 4 TEAEs were reported in up to 94% of patients. The most frequently reported grade 3 / 4 TEAEs were blood and lymphatic system disorders in approximately 85% of patients, mainly cytopenias, including neutropenia (60-65%), anaemia (35%), lymphopenia (30-35%), and thrombocytopenia (25%), while approximately 5% had febrile neutropenia. Infections and infestations of grade 3 / 4 occurred in 40% of patients, mainly COVID-19 (10%) and pneumonia (10%). Grade 3 / 4 hypophosphataemia and hypertension was reported in 8 and 5% of patients, respectively.

Serious TEAEs were reported in up to 64% of patients, with serious TEAEs judged as drug-related in more than one quarter of cases. The most frequently reported serious TEAEs were infections and infestations in 35-40% of patients, mainly COVID-19 (10-15%), pneumonia (10%), sepsis (2-4%), and Pneumocystis jirovecii pneumonia (3%). Approximately 4% developed serious febrile neutropenia, and although approximately 10% experienced serious CRS, only one CRS event was of grade 3. Serious acute kidney injury (AKI) was reported in 4% of patients (no serious AKI was reported in the “Non-RP2D” SC patients), and serious diarrhoea in approximately 3%, however, the incidence of AKI might be confounded by the underlying disease.

Overall, 148 of 340 patients (44%) had died as of DCO in Study MajesTEC-1, with a similar overall mortality in patients treated at RP2D (41%). Of the 148 overall deaths, approximately 63% (93/148)

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died primarily due to progressive disease (27% of all study patients), whereas approximately 24% (36/148) of patients died primarily due to AEs (12% of all patients treated at RP2D). The corresponding proportions of PD- and AE-related deaths in patients treated at RP2D were 60% (50/84) and 30% (25/84), respectively (25% and 12% of all patients, respectively). It is of note that COVID-19-related deaths accounted for 38% (21/55) and 44% (15/34) of non-PD-related deaths in all study patients and all patients treated at RP2D, respectively.

Grade 5 (fatal) AEs were reported for 13% (44/340) of all study patients, and the incidence was highest in patients treated at RP2D (17%, 34/203) compared with other SC dosages and after IV administration (approximately 7%). Fatal infections were the most prevalent grade 5 AEs (7-8% of all patients), reported in the majority (approximately 70%) of patients who primarily died of grade 5 AEs. The most common fatal infection was COVID-19 (5-7% of all patients; 75-80% of all fatal infections), and again the incidence was highest in patients treated at RP2D (7%) as compared to other SC dosages and after IV administration (approximately 2-3.5%). Other reported grade 5 AEs were unspecific (such as general physical health deterioration), and/or reported in single instances only. As compared to the earlier DCO 07 September 2021, nine new Grade 5 TEAEs were reported in subjects treated at pivotal RP2D who died due to AE (preferred terms: COVID-19 [5 subjects] and pneumonia streptococcal, hepatic failure, hypovolaemic shock, and PML [1 subject each]). Besides individual COVID-19 cases, PML and hepatic failure were judged by the investigator as possibly or probably related to Tecvayli.

Evaluation of death rates is challenging as comparator data are lacking and the underlying disease, might have confounded death causes, especially for infections. Furthermore, differences in death rates between Phase 1 and Phase 2 are confounded by small sample sizes of cohorts as well as differences in duration of exposure / follow-up and safety reporting (Phase 1 vs. Phase 2: grade 5 TEAE reporting of PD-related deaths per investigator discretion vs. requested and TEAE window 100 vs. 30 days). In addition, COVID-19-related deaths are an important contributor to the imbalance observed between Phase 1 and Phase 2 and can, at least partly, be explained by an increased COVID-19 risk during the conduct of Phase 2 compared with Phase 1 that was conducted earlier. Overall, death rates do not raise concern when the expected mortality in this population is considered based on historical data and recently approved drugs for the therapy of late relapses of MM. Except for fatal infections, no specific pattern or signal can be detected for grade 5 AEs based on the available safety data as of DCO 16 March 2022.

There was a notable incidence of COVID-19-related deaths in study MajesTEC-1. As of 16 March 2022, approximately 7% (14/203) of all patients treated with Tecvayli at RP2D had died from COVID-19 infections, which means that more than 40% of patients with treatment-emergent COVID-19 infections died from it, despite almost 60% of these patients having received a COVID-19 vaccination and 10% monoclonal antibodies as prophylaxis. In addition, COVID-19-related deaths accounted for almost half (15/34) of all non-progressive-disease-related deaths and approximately 80% of all fatal infections in this population. Overall, incidences of SARS-CoV-2 infection and COVID-19-related fatality appear to be reasonably consistent with rates that could have been expected based on publicly available data. In addition, subsequently submitted preliminary data from MajesTEC-3 suggest rather lower incidences of SARS-CoV-2 infection (11%) and COVID-19-related fatality (no cases reported by the time of submission).

It is of note that three cases of PML have been reported in total in the Tecvayli development programme (N=894, as of 01 July 2022), one of which was in study MajesTEC-1. All three cases were fatal. The estimated incidence of PML is approximately 0.3%. So far, three fatal hepatic events have been reported throughout the Tecvayli development programme for which the involvement of Tecvayli appears probable, i.e. two cases of hepatic failure unrelated to disease progression and one case of hepatitis B-reactivation; estimated incidence is approximately 0.3%. Hepatotoxicity, including fatal outcomes, is a risk associated with Tecvayli, and appears to be secondary to immunologic reactions such as CRS, infections and/or reactivation of latent infections such as (hepatitis) virus reactivation.

Few patients treated with the proposed registrational RP2D dosage of Tecvayli had the dose reduced or discontinued due to TEAE. However, a substantial proportion of patients, up to 70% of patients

treated at RP2D, experienced cycle delay, delay within cycle or dose skipped due to TEAE, most frequently due to infections [up to 35%] (especially due to pneumonia), cytopenias [up to 30%] (especially due to neutropenia) and CRS (up to 12%). In addition, it is of note that, in the “Non-RP2D” SC cohort, which included patients who were dosed at dosages lower than the proposed registrational RP2D dosage, the proportion of patients with TEAEs leading to dose modification was more than 10% lower than at RP2D. This supports the assumption that lower dosages of Tecvayli could be associated with less toxicity.

The proportion of patients who experienced CRS was high, 71% of all patients treated with the RP2D of Tecvayli, particularly as all patients had received premedication including steroids. The most common AEs associated with CRS were pyrexia in almost all patients diagnosed with CRS, followed by chills, hypotension, and hypoxia, each in approximately 10%. However, given that almost all CRS events were of grade 1 and 2 severity, they were manageable without leading to treatment discontinuation, the CRS frequency and severity decreased over time, and considering the poor prognosis of the targeted disease, the CRS-related safety profile is still considered acceptable.

Neurologic AEs were reported in the majority (50-60%) of patients treated with Tecvayli. Frequent AEs included headache (25%), encephalopathy (15%), sensory neuropathy (15%), motor dysfunction (15%), dizziness (5-15%), insomnia (5-10%), and delirium (2-4%). Most neurologic AEs had a maximum severity of Grade 1 or 2; approximately 5% were Grade 3/4 and approximately 5% were serious.

It is of note that one case of parkinsonism was reported after administration of Tecvayli, consisting of cogwheel rigidity, hypokinesia, lethargy, and tremor.

While no Grade 5 neurologic AEs had been reported as of DCO 16 March 2022, subsequently a fatal case of Guillain-Barré syndrome (GBS) was reported in a 67-year old female patient on the RP2D of Tecvayli. No other cases of GBS had been identified in any ongoing Tecvayli study as of 07 July 2022. See “Warnings and precautions” section of the information for healthcare professionals.

As of DCO 16 March 2022, 9 of 203 patients (4.4%) treated at RP2D experienced Grade 1 (6 subjects [3.0%]), Grade 2 (2 subjects [1.0%]) or Grade 3 (1 subject [0.5%]) immune effector cell-associated neurotoxicity syndrome (ICANS). Eleven of the 13 ICANS events (85%) were concurrent with CRS. The most common preferred term associated with ICANS was confusional state (2.0%) followed by aphasia (1.0%) and dysgraphia (1.0%).

Based on available data, Tecvayli demonstrated low risk of immunogenicity. Of the 146 subjects evaluable for the presence of ADAs following the administration of the SC RP2D regimen, none were identified as positive for antibodies to Tecvayli.

Because, as per the protocol of pivotal Study MajesTEC-1, hospitalisation for at least 48 hours was required for all Phase 2 patients after step-up and first treatment dosing, as well as for the subsequent dose of Tecvayli in case of neurotoxicity (Grade ≥2) and CRS (Grade 2/3), pertinent monitoring recommendations have been mandated in the information for healthcare professionals.

6.5 Final clinical and clinical pharmacology benefit risk assessment

Tecvayli has been proposed for the treatment of adult patients with triple-class exposed RRMM who had received at least 3 prior lines of systemic therapy. Historically this patient population has a poor prognosis as reflected by an ORR of approximately 30%, median PFS of approximately 3 to 6 months, and median OS of approximately 6 to 12 months. In addition, alternative therapeutic options are essentially limited to anti-BCMA CAR-T cell therapy, which may however not be suitable/available for all patients. Furthermore, no therapeutic options exist for triple-class exposed RRMM patients, who additionally have received prior anti-BCMA therapy. Taken together, there is substantial medical need for new treatments for the proposed patient population.

In heavily pretreated patients with triple-class exposed RRMM (median of 5 lines of prior therapy) without prior anti-BCMA therapy (CAR T-cell or antibody-drug conjugate) Tecvayli achieved an ORR

of approximately 60%. Compared with historical results for patients with ≥ triple-exposed RRMM, including recently approved non-CAR-T therapies, ORR is approximately doubled. Even in patients with RRMM who had additionally received prior anti-BCMA therapy including CAR T-cells (median of 6 lines of prior therapy), a population for whom no alternative therapies exist, Tecvayli still achieved an ORR of 40%.
Compared with historical data and recently approved drugs for the therapy of late relapses of MM, the updated (DCO 16 March 2022) estimated median PFS and OS of 10 months and 16 months, respectively, observed in the primary pooled Phase 2 population are encouraging and support the promising ORR results.

However, data from only one pivotal Phase 1/2 clinical study have been provided, without the submission of any further supportive clinical data. Furthermore, the pivotal study was conducted open-label, so that relevant biases cannot be excluded. In addition, the interpretation of study results is challenging without a control arm, while cross-study comparisons are prone to bias.

Furthermore, the primary endpoint of ORR used in the pivotal study MajesTEC-1 is not considered an established surrogate parameter for OS. Therefore, ORR results need to be accompanied by convincing evidence demonstrating favourable treatment effects on OS, even more so as the targeted late stage RRMM indication is associated with a poor prognosis and high mortality burden. In spite of this, durations of exposure to Tecvayli and follow-up were short, and time-to-event efficacy endpoints including OS are immature.

The most relevant risks associated with Tecvayli therapy are CRS, neurotoxicity, cytopenias, and infections (including fatal infections such as COVID-19). All these AEs have been observed in substantial proportions of patients treated with Tecvayli.

Overall, interpretation of safety is hampered by the lack of any comparator data in the safety pool, especially as the underlying disease might confound AEs such as cytopenias, infections (including COVID-19) and kidney injury. The limited duration of exposure to Tecvayli, differences in duration of exposure and follow-up across different patient cohorts and study phases, and differences in the safety reporting between Phase 1 and Phase 2 patients in Study MajesTEC-1 further reduce the interpretability of the safety results. In addition, the safety database for this new molecular entity is small, based on a single Phase 1/2 study, and only 203 of 340 patients exposed to Tecvayli were treated with the proposed registrational dosage (RP2D) using the recommended SC route of administration, while many of the remaining patients achieved lower exposures.

Taken together, the current basis of evidence is insufficient for a regular marketing authorisation. Instead, a temporary marketing authorisation *ex officio* supported by the following post-marketing requirements (PMRs) has been considered adequate in light of the medical need, promising efficacy results and the overall manageable safety profile of Tecvayli.

Post-marketing requirements (PMRs) requesting the submission of additional evidence to allow for a conclusive assessment of the benefit-risk ratio of Tecvayli when used per the above indication, have been mandated as a prerequisite for converting the temporary into a regular marketing authorisation. These include the submission of Clinical Study Reports containing updated and current efficacy and safety results from the ongoing studies MajesTEC-1, MajesTEC-3, and MajesTEC-9. The last two are randomised controlled Phase 3 studies enrolling patients with RRMM, for which results were not available at the time of the initial marketing authorisation application. Availability of data from MajesTEC-3 and MajesTEC-9 is considered important, as this will allow the comparison of the efficacy and, in particular, safety of Tecvayli-based therapy versus the respective comparator therapies. Additional PMRs refer to the submission of current summaries of efficacy for other ongoing relevant clinical studies of Tecvayli for the treatment of MM, and the request to submit a current safety analysis of all available data from the Tecvayli development programme.

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7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Tecvayli was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

TECVAYLI has been authorised temporarily, see *Properties/Effects*.

TECVAYLI™

Composition

Active substances

Teclistamab

Excipients

EDTA disodium salt dihydrate, Glacial acetic acid, Polysorbate 20, Sodium acetate trihydrate, Sucrose (240 mg in 3 mL vial; 140 mg in 1.7 mL vial), Water for injection

Total sodium content: 0.75 mg of sodium in 3 mL vial; 0.43 mg of sodium in 1.7 mL vial

Pharmaceutical form and active substance quantity per unit

TECVAYLI is a colorless to light yellow 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)

Indications/Uses

TECVAYLI as monotherapy is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, and have demonstrated disease progression to the last line of therapy (see *Properties/Effects*).

Dosage/Administration

TECVAYLI should only be administered under the guidance of medical personnel experienced in the treatment of malignant haematological diseases, cytokine release syndrome (CRS) and neurological toxicities including immune effector cell-associated neurotoxicity syndrome (ICANS).

Monitoring

Intensive monitoring of patients is recommended in the following cases:

- After each dose of TECVAYLI in the step-up dosing schedule (step-up dose 1, step-up dose 2 and first treatment dose; see table 1, step-up dosing schedule).
- For subsequent TECVAYLI injections, if the patient experiences CRS (grade ≥ 2) or clinically relevant neurological toxicities following the previous dose of TECVAYLI.

In these cases, inpatient monitoring should be provided for at least 48 hours in appropriately equipped centres that have multidisciplinary teams with sufficient experience to provide intensive medical treatment for even the most severe complications. In addition, patients should be monitored daily for signs and symptoms of cytokine release syndrome (CRS), and neurological and other toxicities up to 7 days after TECVAYLI administration (see *Dosage and Administration - Management of severe adverse reactions and Warnings and Precautions*). In addition, patients should be instructed to remain within proximity of a treatment centre during this period. Any further monitoring is at the discretion of the physician.

TECVAYLI should be administered by subcutaneous injection only.
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.
Administer pretreatment medications prior to each dose of the TECVAYLI step-up dosing schedule (see *Dosage and Administration – Pretreatment medications*).

Recommended dosing schedule

Administer TECVAYLI according to the step-up dosing schedule in Table 1 to reduce the incidence and severity of cytokine release syndrome (CRS). 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.
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 of TECVAYLI, 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	
Step-up dosing schedule[a]	Day 1	Step-up dose 1	0.06 mg/kg
	Day 4[b]	Step-up dose 2	0.3 mg/kg
	Day 7[c]	First treatment dose	1.5 mg/kg
Weekly dosing schedule[a]	One week after first treatment dose and weekly thereafter	Subsequent treatment doses	1.5 mg/kg once weekly

[a] See Table 2 for recommendations on restarting TECVAYLI after dose delays *(see Dosage and Administration - Restarting TECVAYLI after dose delays)*.
[b] Step-up dose 2 may be given between 2 to 4 days after step-up dose 1 and may be given up to 7 days after step-up dose 1 to allow for resolution of adverse reactions.
[c] First treatment dose may be given between 2 to 4 days after step-up dose 2 and may be given up to 7 days after step-up dose 2 to allow for resolution of adverse reactions.

Based on the available limited evidence, reduced dosing frequency (treatment every 2 weeks instead of weekly) after confirmed treatment response and at least four cycles of therapy was not associated with inferior efficacy. A lower dose (e.g. 0.72 mg/kg instead of 1.5 mg/kg) was tested during the dose-finding studies and was not associated with a lower response rate.

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 *Undesirable effects*).

- Corticosteroid (oral or intravenous dexamethasone, 16 mg)
- H1-Antihistamine (oral or intravenous diphenhydramine, 50 mg or equivalent)
- Antipyretics (oral or intravenous acetaminophen, 650 mg to 1'000 mg or equivalent)

Administration of pretreatment medications may be required prior to administration of subsequent doses of TECVAYLI in the following patients:

- 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 – Management of severe adverse reactions*)

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 – Recommended dosing schedule)*. Administer pretreatment medications as indicated in Table 2 and monitor patients intensively according to section “Monitoring” following administration of TECVAYLI (see *Dosage and Administration – Pretreatment medications* and *Monitoring*).

Table 2: Recommendations for Restarting Therapy with TECVAYLI After Dose Delay

Last dose administered	Duration of delay from the last dose administered	Action
Step-up dose 1	More than 7 days	Restart TECVAYLI step-up dosing schedule at step-up dose 1 (0.06 mg/kg)[a].
Step-up dose 2	8 days to 28 days	Repeat step-up dose 2 (0.3 mg/kg)[a] and continue TECVAYLI step-up dosing schedule.
	More than 28 days[b]	Restart TECVAYLI step-up dosing schedule at step-up dose 1 (0.06 mg/kg)[a].
Any treatment dose	8 days to 28 days	Continue TECVAYLI weekly dosing schedule at treatment dose (1.5 mg/kg).

Table 2: Recommendations for Restarting Therapy with TECVAYLI After Dose Delay

	More than 28 days[b]	Restart TECVAYLI step-up dosing schedule at step-up dose 1 (0.06 mg/kg)[a].

[a] Administer pretreatment medications prior to TECVAYLI dose and monitor patients accordingly.
[b] Consider benefit-risk of restarting TECVAYLI in patients who require a dose delay of more than 28 days due to an adverse reaction.

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 Tables 3, 4, and 5 for recommended actions for adverse reactions of CRS, neurologic toxicity, and ICANS. See Table 6 for recommended actions for other adverse reactions following administration of TECVAYLI (see *Dosage and Administration – Management of severe adverse reactions*).

Management of severe adverse reactions

Cytokine release syndrome (CRS)

In the clinical trial MajesTEC-1 with TECVAYLI, median time to onset of CRS following last injection of TECVAYLI was 2 (range: 1 to 6) days. 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 3. 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 3: Recommendations for Management of Cytokine Release Syndrome

Grade[a]	Presenting Symptoms	Actions
Grade 1	Temperature ≥ 38°C[b]	• Withhold TECVAYLI until CRS resolves. • Manage CRS per consensus guidelines • Administer pretreatment medications prior to next dose of TECVAYLI.[c]
Grade 2	Temperature ≥ 38°C[b] with: Hypotension responsive to fluids and not requiring vasopressors. and/or Oxygen requirement of low-flow nasal cannula[d] or blow-by.	• Withhold TECVAYLI until CRS resolves. • Manage CRS per consensus guidelines. • Administer pretreatment medications prior to next dose of TECVAYLI.[c] • Patients should be monitored in an inpatient setting for at least 48 hours following the next dose of TECVAYLI[c] *(see Dosage and Administration – Monitoring).*

Grade 3	Temperature ≥ 38°C[b] with: Hypotension requiring one vasopressor with or without vasopressin. and/or Oxygen requirement of high-flow nasal cannula[d], facemask, non-rebreather mask, or Venturi mask.	First Occurrence of Grade 3 CRS with duration less than 48 hours: • Withhold TECVAYLI until CRS resolves. • Manage CRS per consensus guidelines. • Provide supportive therapy, which may include intensive care. • Administer pretreatment medications prior to next dose of TECVAYLI.[c] • Patients should be monitored in an inpatient setting for at least 48 hours following the next dose of TECVAYLI[c] *(see Dosage and Administration – Monitoring).*
		Recurrent Grade 3 CRS or Grade 3 CRS with duration 48 hours or longer: • Permanently discontinue TECVAYLI. • Manage CRS per consensus guidelines. • Provide supportive therapy, which may include intensive care.
Grade 4	Temperature ≥ 38°C[b] with: Hypotension requiring multiple vasopressors (excluding vasopressin). and/or Oxygen requirement of positive pressure (e.g., continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), intubation, and mechanical ventilation).	• Permanently discontinue TECVAYLI. • Manage CRS per consensus guidelines • Provide supportive therapy, which may include intensive care.

[a] Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for CRS.
[b] 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.
[c] See Table 2 for recommendations on restarting TECVAYLI after dose delays (see *Dosage and Administration – Restarting TECVAYLI after dose delays).*
[d] Low-flow nasal cannula is ≤6 L/min, and high-flow nasal cannula is >6 L/min.

Neurologic toxicities and ICANS

In the clinical trial MajesTEC-1 with TECVAYLI, median time to onset of neurologic toxicity (excluding ICANS) was 2 (range: 1 to 38) days after the most recent dose. The median time to onset of ICANS was 3 days (range: 2 to 5) after the most recent dose. Management recommendations for neurologic toxicity and ICANS are summarized in Table 4 and 5.

At the first sign of neurologic toxicity including ICANS, withhold TECVAYLI and 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*). Manage according to the recommendations in Table 4 and 5.

Table 4: Recommendations for Management of Neurologic Toxicity (excluding ICANS)

Adverse Reaction	Severity[a]	Actions
Neurologic Toxicity[a] (excluding ICANS)	Grade 1	• Withhold TECVAYLI until neurologic toxicity symptoms resolve or stabilize.[b]

	Grade 2 Grade 3 (First occurrence)	• Withhold TECVAYLI until neurologic toxicity symptoms improve to Grade 1 or less.[b] • Provide supportive therapy.
	Grade 3 (Recurrent) Grade 4	• Permanently discontinue TECVAYLI. • Provide supportive therapy, which may include intensive care.

[a] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

[b] See Table 2 for recommendations on restarting TECVAYLI after dose delays *(see Dosage and Administration – Restarting TECVAYLI after dose delays)*.

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

Grade[a]	Presenting Symptoms[b]	Actions
Grade 1	ICE score 7-9[c], or depressed level of consciousness[d]: awakens spontaneously.	• Withhold TECVAYLI until ICANS resolves.[e] • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy per consensus guidelines.
Grade 2	ICE score 3-6[c], or depressed level of consciousness[d]: awakens to voice.	• Withhold TECVAYLI until ICANS resolves. • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy per consensus guidelines. • Patients should be monitored in an inpatient setting for at least 48 hours following the next dose of TECVAYLI *(see Dosage and Administration – Monitoring)*[e].
Grade 3	ICE score 0-2[c], or depressed level of consciousness[d]: awakens only to tactile stimulus, or seizures[d], 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[d].	First Occurrence of Grade 3 ICANS: • Withhold TECVAYLI until ICANS resolves. • Administer dexamethasone[f] 10 mg intravenously 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy, which may include intensive care, per consensus guidelines. • Patients should be monitored in an inpatient setting for at least 48 hours

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

Grade[a]	Presenting Symptoms[b]	Actions
		following the next dose of TECVAYLI *(see Dosage and Administration – Monitoring)*[e].
		Recurrent Grade 3 ICANS: • Permanently discontinue TECVAYLI • Administer dexamethasone[f] 10 mg intravenously and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy, which may include intensive care, per consensus guidelines.
Grade 4	ICE score 0[c], or depressed level of consciousness[d]: either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures[d], either: • life-threatening prolonged seizure (>5 minutes), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings[d]: • deep focal motor weakness such as hemiparesis or paraparesis, or raised intracranial pressure/cerebral edema[d], 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.	• Permanently discontinue TECVAYLI. • Administer dexamethasone[f] 10 mg intravenously and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Alternatively, consider administration of methylprednisolone 1'000 mg per day intravenously and continue methylprednisolone 1'000 mg per day intravenously for 2 or more days. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy, which may include intensive care, per consensus guidelines.

[a] Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for ICANS.
[b] Management is determined by the most severe event, not attributable to any other cause.
[c] 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.
[d] Not attributable to any other cause.
[e] See Table 2 for recommendations on restarting TECVAYLI after dose delays *(see Dosage and Administration– Restarting TECVAYLI after dose delays).*
[f] All references to dexamethasone administration are dexamethasone or equivalent.

Other Adverse Reactions

Table 6: Recommended Dosage Modifications for Other Adverse Reactions

Adverse Reactions	Severity	Actions
Infections[a] *(see Warnings and Precautions)*	All Grades	• Withhold TECVAYLI in patients with active infection during the step-up dosing schedule.[b]
	Grade 3	• Withhold subsequent treatment doses of TECVAYLI (i.e., doses administered after TECVAYLI step-up dosing schedule) until infection improves to Grade 1 or less.[b]
	Grade 4	• Consider permanent discontinuation of TECVAYLI. • If TECVAYLI is not permanently discontinued, withhold subsequent treatment doses of TECVAYLI (i.e., doses administered after TECVAYLI step-up dosing schedule) until infection improves to Grade 1 or less.[b]
Hematologic Toxicities (see *Warnings and Precautions and Undesirable effects*)	Absolute neutrophil count less than 0.5 x 10^9/L	• Withhold TECVAYLI until absolute neutrophil count is 0.5 x 10^9/L or higher.[b]
	Febrile neutropenia	• Withhold TECVAYLI until absolute neutrophil count is 1 x 10^9/L or higher and fever resolves.[b]
	Hemoglobin less than 8 g/dL	• Withhold TECVAYLI until hemoglobin is 8 g/dL or higher.[b]
	Platelet count less than 25’000/µl Platelet count between 25’000/µl and 50’000/µl with bleeding	• Withhold TECVAYLI until platelet count is 25’000/µl or higher and no evidence of bleeding.[b]
Other Non-Hematologic Adverse Reactions[a] *(Warnings and Precautions and Undesirable effects)*	Grade 3	• Withhold TECVAYLI until adverse reaction improves to Grade 1 or less.[b]
	Grade 4	• Consider permanent discontinuation of TECVAYLI. • If TECVAYLI is not permanently discontinued, withhold subsequent treatment doses of TECVAYLI (i.e., doses administered after TECVAYLI step-up dosing schedule) until adverse reaction improves to Grade 1 or less.[b]

[a] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

[b] See Table 2 for recommendations on restarting TECVAYLI after dose delays *(see Dosage and Administration – Restarting TECVAYLI after dose delays)*.

Special dosage instructions

Patients with hepatic disorders

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*).

Patients with renal disorders

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*).

Elderly patients (65 years of age and older)

Of the 203 patients treated with TECVAYLI in MajesTEC-1 at the recommended dose, 47 % were 65 years of age or older, and 13 % were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. However, the number of patients aged 75 years or older was insufficient to determine differences in safety or efficacy.
No dose adjustment is necessary (see *Pharmacokinetic Properties*).

Pediatric population

TECVAYLI is not authorised for use in the paediatric population.

Contraindications

None.

Warnings and precautions

Cytokine release syndrome (CRS)

TECVAYLI can cause cytokine release syndrome (CRS), including life-threatening or fatal reactions (see Undesirable Effects).

In the clinical trial, CRS occurred in 71 % of patients who received TECVAYLI at the recommended dose, with Grade 1 CRS occurring in 51 % of patients, Grade 2 in 20 %, and Grade 3 in 0.5 %. Recurrent CRS occurred in 33 % of patients. Most patients experienced CRS following step-up dose 1 (42 %), step-up dose 2 (36 %), or the initial treatment dose (25 %). Two percent of patients developed first occurrence of CRS following subsequent doses of TECVAYLI. 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, acute 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 -Monitoring*). In patients who experienced CRS following their previous dose, administer pretreatment medications prior to the next dose of TECVAYLI and perform intensive monitoring.
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 based on severity. Withhold treatment with TECVAYLI until CRS resolves as indicated in Table 3 (see *Dosage and Administration - Management of severe adverse reactions*).

Neurologic toxicities including ICANS

TECVAYLI can cause serious or life-threatening neurologic toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) (see *Undesirable Effects*).
In the clinical trial at the recommended dose, neurologic toxicity (including ICANS) occurred in 56 % of patients who received TECVAYLI at the recommended dose, with Grade 3 or 4 neurologic toxicity occurring in 4 % of patients. With longer follow-up, Grade 4 seizure and fatal Guillain-Barré syndrome (one patient each) occurred in patients who received TECVAYLI. For described cases of progressive multifocal leukoencephalopathy (PML), see *Infections*.
In the clinical trial, ICANS was reported in 4.4 % of patients who received TECVAYLI at the recommended dose. Recurrent ICANS occurred in 1 % of patients. Most patients experienced ICANS following step-up dose 1 (1.0 %), step-up dose 2 (1.0 %), or the initial treatment dose (1.5 %). Less than 2 % of patients developed first occurrence of ICANS following subsequent doses of TECVAYLI. The median time to onset of ICANS was 3 (range: 2 to 5) days after the most recent dose with a median duration of 2 (range: 1 to 20) days.
The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.
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*).
For ICANS or other neurologic toxicities, withhold treatment with TECVAYLI as indicated in Table 4 and 5 and manage adverse reactions based on recommendations in Table 4 and 5.

Infections

Severe, life-threatening or fatal infections, including opportunistic infections, have been reported in patients receiving TECVAYLI (see *Undesirable Effects*).
In patients who received TECVAYLI at the recommended dose in the clinical trial, opportunistic infections occurred in 9.4 % of patients, with Grade 3 or higher infections in 6.4 %.

Fatal cases of progressive multifocal leukoencephalopathy (PML) were observed across the TECVAYLI development program.
New or reactivated viral infections occurred during therapy with TECVAYLI (see Undesirable Effects).
In patients who received TECVAYLI at the recommended dose in the clinical trial, COVID-19 occurred in 17 % of patients, with Grade 3 or 4 COVID-19 infections in 5.4 %, and fatal infections in 6.9 %.
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.
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. Withhold treatment with TECVAYLI as indicated in Table 6 (see *Dosage and Administration - Dosage modifications*).

Hepatotoxicity

TECVAYLI can cause hepatoxicity, including fatalities. In patients who received TECVAYLI at the recommended dose in the clinical trial, there was one fatal case of hepatic failure.
Monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated. Withhold TECVAYLI or consider permanent discontinuation of TECVAYLI based on severity and manage per local institutional guidelines (see Dosage and Administration – Dosage modifications).

Hypogammaglobulinemia

Hypogammaglobulinemia has been reported in patients receiving TECVAYLI (see *Undesirable Effects*).
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 *Undesirable Effects*).

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 6 (see *Dosage and Administration - Dosage modifications*).

Hypersensitivity and other administration reactions

TECVAYLI can cause both systemic administration-related reactions and local injection-site reactions.

Systemic Reactions

In patients who received TECVAYLI at the recommended dose in the clinical trial, 1.0 % of patients experienced systemic-administration reactions, which included Grade 1 recurrent pyrexia and Grade 1 swollen tongue.

Local Reactions

In patients who received TECVAYLI at the recommended dose in the clinical trial, injection-site reactions occurred in 39 % of patients, with Grade 1 injection-site reactions in 35 % and Grade 2 in 4.4 %.
Withhold TECVAYLI or consider permanent discontinuation of TECVAYLI based on severity (see *Dosage and Administration, Other Adverse Reactions)*.

Excipients

TECVAYLI contains less than 1 mmol sodium (23 mg) per 1 vial, i.e. it is almost "sodium-free".

Patient populations not studied in clinical trials

The following patient groups were excluded from the MajesTEC-1 study: Patients with hypercalcemia (> 3.5 mmol/L), renal insufficiency (serum creatinine > 1.5 mg/dL or creatinine clearance < 40 mL/min), anemia (hemoglobin < 80 g/L), ECOG performance status > 1, CNS involvement, other plasma cell / monoclonal protein disorders, infections (HIV, AIDS, HBV, HCV) / autoimmune diseases (with the exception of vitiligo, Type 1 diabetes and prior autoimmune thyroiditis), cardiac disorders (congestive heart failure NYHA class III or IV, myocardial infarction or CABC ≤ 6 months prior to enrollment, history of clinically significant ventricular arrhythmia or unexplained syncope, history of severe non-ischemic cardiomyopathy), stroke or seizure within the last six months and patients who have received live, attenuated vaccines within 4 weeks prior to the first dose of TECVAYLI.

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. CYP450 substrates with a narrow therapeutic index should be used with caution in

patients receiving TECVAYLI. Monitor for toxicity (e.g., warfarin) or drug concentrations (e.g., cyclosporine) for 48 hours after administration of all doses within the TECVAYLI step-up dosing schedule and for patients who develop cytokine release syndrome (see *Warnings and Precautions – Cytokine Release Syndrome*). The dose of the concomitant drug should be adjusted as needed.

Pregnancy, lactation

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.

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 immunoglobulin G (IgG) is known to cross the placenta. Therefore, teclistamab has the potential to be transmitted from the mother to the developing fetus. TECVAYLI induces T-cell activation and cytokine release, which may adversely affect the course of pregnancy. TECVAYLI should not be administered to pregnant women unless clearly indicated. TECVAYLI is associated with hypogammaglobulinemia, therefore, assessment of immunoglobulin levels in newborns of mothers treated with TECVAYLI should be considered.

Lactation

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.

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 neurologic events, 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 (see *Dosage and Administration*, Table 1) and in the event of new onset of any neurological symptoms until neurologic toxicity resolves.

Undesirable effects

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.

Summary of the safety profile

The safety data of TECVAYLI was evaluated in MajesTEC-1, which included 203 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 7.8 (Range: 0.2 to 24.4) months.
The most frequent adverse reactions of any grade (≥ 20 %) in patients were hypogammaglobulinemia (75 %), cytokine release syndrome (71 %), neutropenia (71 %), anaemia (54 %), musculoskeletal pain (52 %), thrombocytopenia (41 %), injection site reaction (40 %), fatigue (40 %), lymphopenia (36 %), upper respiratory tract infection (35 %), fatigue (35 %), diarrhoea (30 %), pyrexia (29 %), pneumonia (26 %), nausea (24 %), headache (24 %) constipation (23 %), cough (22 %), and pain (20 %).
Serious adverse reactions were reported in 64 % patients who received TECVAYLI. Serious adverse reactions reported in ≥ 2 % of patients included COVID-19 (14 %), pneumonia (14 %), cytokine release syndrome (8 %), sepsis (6 %), musculoskeletal pain (6 %), pyrexia (4.9 %), acute kidney injury (4.4 %), febrile neutropenia (3.4 %), diarrhoea (3 %), cellulitis (2 %), hypoxia (2 %) and encephalopathy (2 %).
Dose interruptions (dose delays and dose skips) of TECVAYLI due to adverse reactions occurred in 66 % of patients. The most frequent adverse reactions (≥ 5 %) leading to dose interruptions were neutropenia (27 %), COVID-19 (11 %), pneumonia (8 %), cytokine release syndrome (8 %) and pyrexia (8 %).
Dose reduction of TECVAYLI due to adverse reaction occurred in one patient (0.5 %) due to neutropenia.
Permanent discontinuation of TECVAYLI due to adverse reactions occurred in two patients (1 %), both due to infection.

List of adverse reactions

Table 7 summarizes adverse reactions reported in patients who received TECVAYLI.

Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000); not known (frequency cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing frequency.

Table 7: Adverse Reactions in Multiple Myeloma Patients Treated with TECVAYLI in MajesTEC-1

System Organ Class	Adverse Reaction	Frequency (all grades)	N=203	
			Incidence (%)	
			Any Grade	Grade 3 or higher
Infections and infestations	Upper respiratory tract infection[1]	Very common	71 (35 %)	4 (2.0 %)
	Pneumonia[2]	Very common	52 (26 %)	34 (17 %)
	COVID-19[3]	Very common	35 (17 %)	25 (12 %)
	Sepsis[4]	Common	15 (7.4 %)	13 (6.4 %)
	Cellulitis	Common	7 (3.4 %)	5 (2.5 %)
	Progressive multifocal leukoencephalopathy (PML)	Uncommon	1 (0.5 %)	1 (0.5 %)
Blood and lymphatic system disorders	Neutropenia	Very common	144 (71 %)	131 (65 %)
	Anemia[5]	Very common	110 (54 %)	74 (36 %)
	Thrombocytopenia	Very common	84 (41 %)	47 (23 %)
	Lymphopenia	Very common	73 (36 %)	69 (34 %)
	Leukopenia	Very common	34 (17 %)	15 (7.4 %)
	Febrile neutropenia	Common	10 (4.9 %)	8 (3.9 %)
Immune system disorders	Hypogammaglobulinaemia[6]	Very common	153 (75 %)	3 (1.5 %)
	Cytokine release syndrome	Very common	144 (71 %)	1 (0.5 %)
Metabolism and nutrition disorders	Hypokalaemia	Very common	28 (14 %)	10 (4.9 %)
	Decreased appetite	Very common	24 (12 %)	1 (0.5 %)
	Hypophosphataemia	Very common	24 (12 %)	13 (6.4 %)
	Hypomagnesaemia	Very common	23 (11 %)	0
	Hypercalcaemia	Common	20 (9.9 %)	5 (2.5 %)
	Hyponatraemia	Common	20 (9.9 %)	11 (5.4 %)
	Hypocalcaemia	Common	18 (8.9 %)	0
	Hyperkalaemia	Common	11 (5.4 %)	2 (1.0 %)
	Hypoalbuminaemia	Common	9 (4.4 %)	2 (1.0 %)
	Hyperamylasaemia	Common	6 (3.0 %)	4 (2.0 %)
Nervous system disorders	Headache	Very common	48 (24 %)	1 (0.5 %)
	Neuropathy peripheral[7]	Very common	29 (14 %)	1 (0.5 %)
	Encephalopathy[8]	Common	18 (8.9 %)	0
	Immune effector cell-associated neurotoxicity syndrome	Common	9 (4.4 %)	1 (0.5 %)
Vascular disorders	Hypertension[9]	Very common	25 (12 %)	10 (4.9 %)
	Hemorrhage[10]	Very common	24 (12 %)	5 (2.5 %)
Respiratory, thoracic and mediastinal disorders	Cough[11]	Very common	44 (22 %)	0
	Dyspnea[12]	Very common	32 (16 %)	4 (2.0 %)
	Hypoxia	Common	17 (8.4 %)	7 (3.4 %)
Gastrointestinal disorders	Diarrhoea	Very common	61 (30 %)	7 (3.4 %)
	Nausea	Very common	49 (24 %)	1 (0.5 %)
	Constipation	Very common	47 (23 %)	0
	Vomiting	Very common	25 (12 %)	1 (0.5 %)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[13]	Very common	106 (52 %)	16 (7.9 %)
	Fatigue[14]	Very common	81 (40 %)	7 (3.4 %)
	Injection site reaction[15]	Very common	81 (40 %)	1 (0.5 %)

General disorders and administration site conditions	Pyrexia	Very common	58 (29 %)	1 (0.5 %)
	Pain[16]	Very common	41 (20 %)	3 (1.5 %)
	Edema[17]	Very common	30 (15 %)	0
Investigations	Transaminase elevation[18]	Very common	23 (11 %)	5 (2.5 %)
	Blood alkaline phosphatase increased	Very common	21 (10 %)	5 (2.5 %)
	Gamma-glutamyltransferase increased	Common	20 (9.9 %)	7 (3.4 %)
	Blood creatinine increased	Common	11 (5.4 %)	0
	Lipase increased	Common	11 (5.4 %)	2 (1.0 %)

Adverse events are coded using MedDRA Version 24.0.
Note: The output includes the diagnosis of CRS and ICANS; the symptoms of CRS or ICANS are excluded.
[1]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.
[2]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.
[3]COVID-19 includes Asymptomatic COVID-19, COVID-19 and COVID-19 pneumonia.
[4]Sepsis includes Bacteraemia, Meningococcal sepsis, Neutropenic sepsis, Pseudomonal bacteraemia, Pseudomonal sepsis, Sepsis and Staphylococcal bacteraemia.
[5]Anemia includes Anaemia, Iron deficiency and Iron deficiency Anaemia.
[6]Hypogammaglobulinaemia includes patients with adverse events of hypogammaglobulinaemia, hypoglobulinaemia, immunoglobulins decreased; and/or patients with laboratory IgG levels below 500 mg/dL following treatment with teclistamab.
[7]Neuropathy peripheral includes Dysaesthesia, Hypoaesthesia, Hypoaesthesia oral, Neuralgia, Paraesthesia, Paraesthesia oral, Peripheral sensory neuropathy and Sciatica.
[8]Encephalopathy includes Confusional state, Depressed level of consciousness, Lethargy, Memory impairment and Somnolence.
[9]Hypertension includes Essential hypertension and Hypertension.
[10]Hemorrhage includes Conjunctival haemorrhage, Epistaxis, Haematoma, Haematuria, Haemoperitoneum, Haemorrhoidal haemorrhage, Lower gastrointestinal haemorrhage, Melaena, Mouth haemorrhage and Subdural haematoma.
[11]Cough includes Allergic cough, Cough, Productive cough and Upper-airway cough syndrome.
[12]Dyspnea includes Acute respiratory failure, Dyspnoea and Dyspnoea exertional.
[13]Musculoskeletal pain includes Arthralgia, Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal pain, Myalgia, Neck pain and Pain in extremity.
[14]Fatigue includes Asthenia, Fatigue and Malaise.
[15]Injection site reaction includes Injection site bruising, Injection site cellulitis, Injection site discomfort, Injection site erythema, Injection site haematoma, Injection site induration, Injection site inflammation, Injection site oedema, Injection site pruritus, Injection site rash, Injection site reaction and Injection site swelling.
[16]Pain includes Ear pain, Flank pain, Groin pain, Non-cardiac chest pain, Oropharyngeal pain, Pain, Pain in jaw, Toothache and Tumour pain.
[17]Edema includes Face oedema, Fluid overload, Oedema peripheral and Peripheral swelling.
[18]Transaminase elevation includes Alanine aminotransferase increased and Aspartate aminotransferase increased.

Description of specific adverse reactions and additional information

Cytokine release syndrome

In MajesTEC-1 (N=203), CRS was reported in 71 % 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 (42 %), step-up dose 2 (36 %), or the initial treatment dose (25 %). Two percent of patients developed first occurrence of CRS following subsequent doses of TECVAYLI. The most frequent (≥ 3 %) signs and symptoms associated with CRS were fever (70 %), hypoxia (12 %), chills (12 %), hypotension (11 %), sinus tachycardia (8 %), headache (6 %), and elevated liver enzymes (aspartate aminotransferase and alanine aminotransferase elevation) (3 % each).

Neurologic toxicities

In MajesTEC-1 (N=203), neurologic toxicities were reported in 56 % of patients receiving TECVAYLI. Most neurologic toxicity events were Grade 1 (28 %) and Grade 2 (25 %). The most frequently

reported neurologic toxicity were headache (24 %), encephalopathy (8 %), insomnia (7 %), confusional state (5 %), dizziness (5 %) and peripheral sensory neuropathy (5 %).
ICANS was reported in 4.4 % of patients receiving TECVAYLI at the recommended dose. The most frequent clinical manifestations of ICANS reported were confusional state (2 %), aphasia (1 %) and dysgraphia (1 %).

Infections

In MajesTEC-1 (N=203), opportunistic infections occurred in 9.4 % of patients with Grade 3 or higher infections in 6.4 %. The most common opportunistic infection was Pneumocystis jirovecii pneumonia (3.4 %). In addition, three fatal cases of progressive multifocal leukoencephalopathy (PML) were observed in the TECVAYLI development programme, including one case in the MajesTEC-1 study (0.5 %). New or reactivated viral infections occurring during therapy with TECVAYLI included adenovirus (1.5 %), hepatitis B virus (HBV) (0.5 %), cytomegalovirus (CMV) (0.5 %), and herpes simplex virus (HSV) (1 %).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms

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.

Properties/Effects

ATC code

L01F

Mechanism of action

Teclistamab is a bispecific IgG4 antibody that targets the CD3 receptor expressed on the surface of T cells and B cell maturation antigen (BCMA), which is expressed mainly on the surface of malignant multiple myeloma B-lineage cells, as well as late-stage B cells and plasma cells. Binding to T cells and BCMA results in T cell activation and subsequent lysis of $BCMA^+$ cells.

Pharmacodynamics

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.

Immunogenicity

Patients treated with subcutaneous teclistamab monotherapy (N=219) in MajesTEC-1 were evaluated for antibodies to teclistamab using an electrochemiluminescence-based immunoassay. One patient (0.5 %) developed antibodies to teclistamab of low-titer which were neutralizing. No patients treated with the recommended dose of TECVAYLI developed antibodies to teclistamab.

Effect on QT/QTc interval and cardiac electrophysiology

No clinical QT study has been conducted. At the recommended treatment dose (1.5 mg/kg) of TECVAYLI, no clinically relevant QTc prolongation has been reported.

Clinical efficacy

The efficacy of TECVAYLI monotherapy was evaluated in patients with relapsed or refractory multiple myeloma in a single-arm, open-label, multicenter, study (MajesTEC-1). The study included patients who had previously received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. The study excluded patients with hypercalcemia (> 3.5 mmol/L), renal insufficiency (serum creatinine > 1.5 mg/dL or creatinine clearance < 40 mL/min), anemia (hemoglobin < 80 g/L), ECOG performance status > 1, CNS involvement, other plasma cell / monoclonal protein disorders, infections (HIV, AIDS, HBV, HCV) / active or documented history of autoimmune diseases (with the exception of vitiligo, Type 1 diabetes and prior autoimmune thyroiditis), cardiac disorders (congestive heart failure NYHA class III or IV, myocardial infarction or CABC ≤ 6 months prior to enrollment, history of clinically significant ventricular arrhythmia or unexplained syncope, history of severe non-ischemic cardiomyopathy),stroke or seizure within the last six months and patients who have received live, attenuated vaccines within 4 weeks prior to the first dose of TECVAYLI.

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*).
The efficacy population included 163 patients, consisting of 125 patients without prior anti-BCMA therapy and 38 patients with prior anti-BCMA therapy. The median age was 64 (Range: 32-83) years with 13 % of patients ≥ 75 years of age; 58 % were male; 82 % were White, 14 % were Black, 2 % were Asian. The International Staging System (ISS) at study entry was 50 % in Stage I, 34 % in Stage II, and

16 % in Stage III. High-risk cytogenetics (presence of del(17p), t(4;14) or t(14; 16)) were present in 26 % of patients. 19 % of patients had extramedullary plasmacytomas.
The median time since initial diagnosis of multiple myeloma to enrollment was 6.4 (Range: 0.9-24.1) years. The median number of prior lines of therapy was 5 (range: 2-14) with 20 % of patients who received 3 prior lines of therapy and 79 % were triple-class refractory (refractory to PI, an IMiD agent and an anti-CD38 monoclonal antibody). 83 % of patients received prior stem cell transplantation, 23 % received prior anti-BCMA therapy (27/38 patients received antibody drug conjugate (ADC) and 15/38 patients received chimeric antigen receptor T cells (CAR-T)).
The median duration of exposure was 4.6 (range: 0.03 to 10.15) months, the median duration of follow-up was 6.4 (range: 0.03 to 10.71) months.
Efficacy results were based on overall response rate (ORR, primary endpoint) as determined by the Independent Review Committee (IRC) assessment using International Myeloma Working Group (IMWG) 2016 criteria (see Table 8, cut-off date 07 September 2021).

Table 8: Efficacy Results for MajesTEC-1

	N=163
Overall response rate (ORR: sCR+CR+VGPR+PR) n (%)	93 (57 %)
95 % CI (%)	(49.1 %, 64.8 %)
Complete response or better[a]	33 (20 %)
Very good partial response (VGPR)	47 (29 %)
Partial response (PR)	13 (8 %)

[a] Complete response or better = Stringent complete response (sCR) + complete response (CR)

In a separate evaluation of the primary endpoint for patients without prior anti-BCMA therapy (n=125) the ORR was 61.6 % (77/125; 95 % CI: 52.5 %, 70.2 %), and 42.1 % (16/38; 95 % CI: 26.3 %, 59.2 %) for patients with prior anti-BCMA therapy, at a median follow-up of 6.5 and 6.1 months respectively.

At an updated clinical cut-off of 16 March 2022 at a median follow-up of 12.7 months, the median time to first response (TTR) was 1.2 months (range: 0.2 to 5.5 months), the median duration of response (DOR) was 14.9 months (95 % CI: 14.9 to NE (not estimable)) and the median progression free survival (PFS) was 8.8 months (95 % CI: 5.8 to 11.5) in the overall efficacy population (N=163). Estimated median overall survival (OS) was not mature at 16.0 months (95 % CI: 12.2 to NE).

At the updated clinical cut-off, in patients without prior exposure to an anti-BCMA therapy (N=125) at a median follow-up of 12.9 months the median TTR was 1.2 months (range: 0.2 to 5.5 months), the median DOR was 14.9 months (95 % CI: 14.9 to NE) and the median PFS was 9.8 months (95 % CI: 6.8 to 16.0). Estimated median OS was not mature at 16.0 months (95 % CI: 12.1 to NE).

At the updated clinical cut-off, in patients with prior anti-BCMA therapy (N=38) at a median follow-up of 12.5 months the median TTR was 1.2 months (range: 0.2 to 4.9 months), the median DOR was not

estimable and the median PFS was 4.5 months (95 % CI: 1.3 to NE). Estimated median OS was not mature at 14.4 months (95 % CI: 8.3 to NE).

Temporary authorisation

Due to incomplete clinical data at the time of the evaluation of the marketing authorisation application, TECVAYLI is granted a temporary marketing authorisation (Art. 9a Therapeutic Products Act). The temporary marketing authorisation is compulsorily linked to the timely fulfilment of conditions. Once these conditions have been fulfilled, the temporary marketing authorisation can be converted into a full marketing authorisation.

Pharmacokinetics

Absorption

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 steady state (based on 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 9.

Table 9: 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 (steady state)
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 4.09 L (31.0 % coefficient of variation (CV)) for the central compartment and 1.29 litre for the peripheral compartment

Metabolism

No data.

Elimination

Teclistamab exhibited both time-independent and time-dependent clearance. Based on the population pharmacokinetic model, the mean time-independent clearance was 0.545 L/day (49.4 % CV), with the median of time-dependent clearance contributing approximately 31 % of the total clearance at baseline and decreasing rapidly thereafter to less than 5 % after week 8.
Based on non-compartmental analysis, the mean half-life (standard deviation) was 3.8 (1.7) days (individual values ranging up to 8.8 days) following the first treatment intravenous dose.
Population pharmacokinetic analysis (based on MajesTEC-1) showed that soluble BCMA did not impact teclistamab serum concentrations

Kinetics in specific patient groups

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 did not significantly influence the pharmacokinetics of teclistamab. Patients with moderate and severe hepatic impairment were not studied.

Renal impairment

No formal studies of TECVAYLI in patients with renal impairment have been conducted.
Results of population pharmacokinetic analyses indicate that mild or moderate renal impairment did not significantly influence the pharmacokinetics of teclistamab. Limited data are available from patients with severe renal impairment.

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.

Preclinical data

No effects on clinical or immunological parameters and safety pharmacology were seen in the 5-week toxicity study in cynomolgus monkeys with weekly intravenous administration of doses up to 30 mg/kg/week (equivalent to 22 times the maximum recommended human dose based on AUC exposure). Due to the lower binding affinity to monkey BCMA compared to human BCMA, and lack of pharmacodynamic activity at clinically relevant doses, clinical safety margins cannot be established from the nonclinical studies and the study cannot adequately inform on safety in humans

Carcinogenicity/Mutagenicity

No genotoxicity or carcinogenicity studies have been performed.

Reproductive toxicity

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

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

Chemical and physical in-use stability of TECVAYLI after drawing up in the ready-to-use syringe (PP, PC) has been demonstrated for 20 hours at 2-8°C in the refrigerator and at room temperature (15-30°C). For microbiological reasons, TECVAYLI should be used immediately after opening, unless controlled and validated aseptic conditions have been applied. If TECVAYLI is not used immediately after opening, storage times and conditions are the responsibility of the user.
Discard after 20 hours, if not used.

Special precautions for storage

Store in the refrigerator (2-8°C).
Store in the original carton in order to protect from light.
Do not freeze.
Keep out of the sight and reach of children.

Instructions for handling

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

Mode of administration

TECVAYLI solution for injection for subcutaneous use is colorless to light yellow. 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 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 10 and Table 11 to determine total dose, injection volume and number of vials required based on patient's actual body weight for step-up dose 1 or step-up dose 2 using TECVAYLI 10 mg/mL vial.
  - Use Table 12 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 vial.

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

Patient Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial = 3 mL)
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

Table 11: Injection Volumes of TECVAYLI 10 mg/mL Vial for Step-up Dose 2 (0.3 mg/kg)

Patient Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial = 3 mL)
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

Table 12: Injection Volume of TECVAYLI 90 mg/mL Vial for Treatment Dose (1.5 mg/kg)

Patient Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial = 1.7 mL)

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 [2-8°C] and equilibrate to ambient temperature [15-30°C] 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.

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.

Authorisation number

68747 (Swissmedic)

Packs

Carton with 1 vial of 30 mg/3 mL (Step-up Dose) [A].
Carton with 1 vial of 153 mg/1.7 mL (Treatment Dose) [A].

Marketing authorisation holder

Janssen-Cilag AG, Zug, ZG

Date of revision of the text

December 2022