Summary of the Risk Management Plan (RMP) for TECVAYLI™ (Teclistamab)

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of TECVAYLI™ is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, eg. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of TECVAYLI™ in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Janssen-Cilag AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of TECVAYLI™.

Summary of Risk Management Plan for teclistamab

This is a summary of the risk management plan (RMP) for TECVAYLI. The RMP details important risks of TECVAYLI, how these risks can be minimized, and how more information will be obtained about TECVAYLI's risks and uncertainties (missing information).

TECVAYLI's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how TECVAYLI should be used.

This summary of the RMP for TECVAYLI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of TECVAYLI's RMP.

I. The Medicine and What it is Used For

TECVAYLI is indicated as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy (see SmPC for the full indication). It contains teclistamab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of TECVAYLI's benefits can be found in TECVAYLI's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of TECVAYLI, together with measures to minimize such risks and the proposed studies for learning more about TECVAYLI's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

In the case of TECVAYLI, these measures are supplemented with an additional risk minimization measure as mentioned under relevant important risks, below.

- Patient card

If important information that may affect the safe use of TECVAYLI is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of TECVAYLI are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of TECVAYLI. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Cytokine release syndrome (CRS) Neurologic toxicity Serious infections
Important potential risks	Not applicable
Missing information	Long-term safety

II.B. Summary of Important Risks

Important Identified Risk: Cytokine release syndrome	
Evidence for linking the risk to the medicine	CRS is a known class effect associated with T-cell redirector therapy including bispecific antibodies that bind to CD3. CRS has been reported in subjects treated in the TECVAYLI clinical trial and was identified as an adverse reaction. The risk for CRS and information regarding this adverse reaction are described in the SmPC for TECVAYLI.

	Based on the strength of evidence from the clinical trial data and information from the literature, CRS is considered an important identified risk for TECVAYLI.
Risk factors and risk groups	The risk factors of CRS are not fully identified; however, active infection may increase the severity of CRS. Active infection was an exclusionary criterion in clinical trials.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 • SmPC Section 4.4 • PL Section 2 • PL Section 4 • Usage of a step-up dosing schedule (ie, Step-up dose 1, Step-up dose 2, and initial maintenance dose) to reduce the incidence and severity of CRS is described in SmPC Sections 4.2 and 4.4. • Instructions that pretreatment medications (corticosteroid, antihistamine, antipyretics) must be administered prior to each dose in the step-up dosing schedule to reduce the risk of CRS are provided in SmPC Sections 4.2 and 4.4. • Instruction for patients to remain within the proximity of a healthcare facility and be monitored daily for 48 hours after administration of all doses in the step-up dosing schedule is provided in SmPC Sections 4.2 and 4.4. • Recommendation to withhold TECVAYLI until any Grade 1, Grade 2, or Grade 3 (<48 hours' duration) CRS event resolves is provided in SmPC Section 4.2 and Section 4.4. • Recommendation to permanently discontinue TECVAYLI for any Grade 3 (recurrent or >48 hours' duration) or Grade 4 CRS event is provided in SmPC Section 4.2. • Recommendation to administer pretreatment medication prior to the next dose for any patient with a CRS event of Grade 1, Grade 2, or Grade 3 (<48 hours' duration) is provided in SmPC Section 4.2 and in SmPC Section 4.4. • For patients who have a CRS event of Grade 2 or Grade 3 (<48 hours' duration), instruction that they should remain within the proximity of a healthcare facility and be monitored daily for 48 hours after the next dose is provided in SmPC Sections 4.2 and 4.4. • Recommendations that patients should be counselled to seek medical attention if signs and symptoms of CRS occur, that patients should be immediately evaluated for hospitalization at the first sign of CRS, and that treatment should be instituted are provided in SmPC Section 4.4.

	• Recommendation to avoid the use of myeloid growth factors, particularly GM-CSF, during CRS is provided in SmPC Section 4.4. • Recommendations that CRS should be identified based on clinical presentation, and that other causes of fever, hypoxia, and hypotension should be evaluated and treated, are provided in SmPC Section 4.4. • Recommendation to administer supportive care as appropriate is provided in SmPC Section 4.4. • Recommendation that laboratory testing should be considered to monitor for disseminated intravascular coagulation, hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function is provided in SmPC Section 4.4. • Specific guidelines for the management of CRS with tocilizumab and/or corticosteroids, depending on toxicity grade and symptoms, is provided in tabular format in SmPC Section 4.4. • Patients should get medical help right away if signs of CRS occur, as described in PL Sections 2 and 4. • The design of the packaging has been chosen to appropriately differentiate between the product strengths to ensure the medicine is used correctly during step-up dosing (where the 10 mg/mL vial should be used). Step-up dosing is designed to mitigate the severity of CRS. Additional risk minimization measures • Patient Card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 64007957MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma See section II.C of this summary for an overview of the postauthorization development plan.
Important Identified Risk: Neurologic toxicity	
Evidence for linking the risk to the medicine	Neurologic toxicity, primarily ICANS, is a known class effect associated with bispecific T-cell redirectors. Neurologic toxicity has been reported in subjects treated with TECVAYLI in the clinical trial and ICANS was identified as an adverse reaction. The risk for neurologic toxicity and information regarding this adverse reaction (including ICANS), are described in the SmPC for TECVAYLI. Based on the known class effect and the evidence from clinical trial data, neurologic toxicity is considered an important identified risk for TECVAYLI.

Risk factors and risk groups	Risk factors have not been fully identified. Patients with CNS disorders may be at higher risk for neurological adverse events.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7 • PL Section 2 • PL Section 4 • Recommendation to withhold TECVAYLI until any Grade 1, Grade 2, or first occurrence of a Grade 3 ICANS event resolves is provided in SmPC Section 4.2. • Recommendation to permanently discontinue TECVAYLI in the case of any recurrent Grade 3 or any Grade 4 ICANS event is provided in SmPC Section 4.2. • Instruction for patients to remain within the proximity of a healthcare facility and be monitored daily for 48 hours after administration of the next dose of TECVAYLI following any Grade 2 or first occurrence of a Grade 3 ICANS event is provided in SmPC Sections 4.2 and 4.4. • Recommendation to monitor patients for signs and symptoms of neurologic toxicity and to treat promptly is provided in SmPC Section 4.4. • Recommendation to counsel patients to seek medical attention if signs or symptoms of neurologic toxicity occur is described in SmPC Section 4.4. • At the first sign of neurologic toxicity (including ICANS), recommendation to immediately evaluate and treat patients, consider neurologic evaluation, and rule out other causes of neurologic symptoms is provided in SmPC Section 4.4. • Recommendation to provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities is provided in SmPC Section 4.4. • Detailed guidelines on the management of ICANS, by severity, symptoms, and whether patients have concurrent CRS, including the use of tocilizumab, corticosteroids, and anti-seizure medications, are provided in tabular format in SmPC Section 4.4. • Recommendation to avoid driving and operating heavy or potentially dangerous machinery during and for 48 hours after completion of the TECVAYLI step-up dosing schedule, and in the event of new onset of any neurological symptoms, is provided in SmPC Sections 4.4 and 4.7.

	• Patients should get medical help right away if symptoms of ICANS or other neurologic toxicities occur, as described in PL Sections 2 and 4. Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 64007957MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma See section II.C of this summary for an overview of the postauthorization development plan.
Important Identified Risk: Serious infections	
Evidence for linking the risk to the medicine	Serious bacterial, fungal, and viral infections, including life-threatening or fatal infections, have been reported for subjects treated with TECVAYLI in the clinical trial and serious infections such as pneumonia and sepsis have been identified as an adverse reaction. The risk for serious infection and information regarding this adverse reaction are described in the SmPC for TECVAYLI. Based on the findings from the clinical trial, serious infections are considered an important identified risk for TECVAYLI. Further data are needed to establish whether a causal relationship exists.
Risk factors and risk groups	There are multiple factors that may increase the risk of infectious complications. Patients with multiple myeloma are at risk of infection due to the overproduction of ineffective monoclonal antibodies from the underlying disease, which causes immune dysfunction. Multiple myeloma patients have as much as a 15-fold increase in risk of infections, particularly pneumonia. In addition, the functional status and medical fragility of the patient may be a risk factor. Studies have shown that hospitalized patients, those with poor functional status or comorbid conditions, and older adults are more likely to develop infection complications. Another risk factor is the concomitant use of other immunosuppressive medications with synergistic adverse immunologic effects. The use of multiple chemotherapy and immunosuppressive treatments (eg, corticosteroids), and neutropenia as a complication of the treatments, increases the risk of infection. In addition, B-cell aplasia and subsequent hypogammaglobulinemia are on-target, off-tumor toxicities for TECVAYLI, which could result in increased susceptibility to infection including reactivation of latent hepatitis B infection.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 • SmPC Section 4.4

	• PL Section 2 • PL Section 4 • Recommendation to consider antiviral prophylaxis for the prevention of herpes zoster virus reactivation per local institutional guidelines is provided in SmPC Section 4.2. • Recommendation to not administer TECVAYLI step-up dosing schedule in patients with active infection (any grade) until the infection has resolved is provided in SmPC Section 4.2. • Recommendation that for subsequent dosing (ie, after step-up dosing), if patients develop an infection of Grade 3 or 4, then TECVAYLI should be withheld until the infection improves to Grade 2 or better is provided in SmPC Section 4.2. • Recommendations that patients should be monitored for signs and symptoms of infection prior to and during TECVAYLI treatment and treated appropriately, and that prophylactic antimicrobials should be administered according to local institutional guidelines, are described in SmPC Section 4.4. • Recommendation that TECVAYLI should not be administered in patients with active infection and should be withheld for subsequent dosing based on severity of infection is provided in SmPC Section 4.4. • Recommendation that patients with positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation during and for at least 6 months after TECVAYLI treatment is provided in SmPC Section 4.4. • Recommendation that for patients who develop reactivation of HBV, TECVAYLI should be withheld and this should be managed per local institutional guidelines is provided in SmPC Section 4.4. • Recommendation to monitor immunoglobulin levels during TECVAYLI treatment and treat hypogammaglobulinemia according to local institutional guidelines, including infection precautions, antibiotic or antiviral prophylaxis, and administration of immunoglobulin replacement, is included in SmPC Section 4.4. • Recommendations that patients with neutropenia should be monitored for signs of infection, treatment should be withheld based on severity, and blood cell counts should be monitored at baseline and periodically during treatment with supportive care provided per local institutional guidelines, are included in SmPC Section 4.4. • Patients should tell their doctor or nurse if they have any signs of infection, as described in PL Sections 2 and 4.

	Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 64007957MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Long-term safety	
Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 64007957MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma See section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorization:

64007957MMY3001: A Phase 3 Randomized Study Comparing Teclistamab in Combination with Daratumumab SC (Tec-Dara) versus Daratumumab SC, Pomalidomide, and Dexamethasone (DPd) or Daratumumab SC, Bortezomib, and Dexamethasone (DVd) in Participants with Relapsed or Refractory Multiple Myeloma

Purpose of the study: The primary objective is to compare the efficacy of teclistamab in combination with daratumumab SC with that of an investigator's choice of DPd or DVd as assessed by progression-free survival (PFS). Secondary objectives are:

- to assess the safety profile of Tec-Dara (including further characterization of the safety concerns of CRS, neurologic toxicity, and serious infections),
- to assess the immunogenicity of teclistamab and daratumumab,
- to further compare the efficacy of Tec-Dara with DPd/DVd;
- to characterize the PK of teclistamab,
- to compare the patient-reported outcomes (PROs) of Tec Dara with DPd/DVd, and

- to evaluate the efficacy of teclistamab in high-risk molecular subgroups.

64007957MMY1001: A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA x CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma

Purpose of the study: The primary objective in Part 1 (dose escalation) is to identify the proposed RP2D(s) and schedule assessed to be safe for teclistamab. The primary objective in Part 2 (dose expansion) is to characterize the safety and tolerability of teclistamab at the proposed RP2D.

II.C.2. Other Studies in Postauthorization Development Plan

Not applicable.