Tevimbra - Risk Management Plan

Summary of Risk Management Plan (RMP) for Tevimbra (Tislelizumab)

Version number of current RMP: 1.0 dated 11 Jul 2023

Marketing Authorisation Holder: BeiGene Switzerland GmbH

Date: 29 May 2024

VV-PVG-001958 Version 1.0

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 risks as well as to prevent or minimise them.

The RMP summary of Tevimbra 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 medicament" approved and published in Switzerland, e.g., by mentioning risks occurring in populations or indications not included in the Swiss authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of Tevimbra in Switzerland is the "Arzneimittelinformation / Information sur le medicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

BeiGene Switzerland GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Tevimbra.

Summary of risk management plan for Tevimbra (Tislelizumab)

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

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

This summary of the RMP for Tevimbra 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 Tevimbra's RMP.

I. The medicine and what it is used for

Tevimbra, as monotherapy, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic esophageal squamous cell carcinoma (ESCC) after prior platinum-based chemotherapy.

It contains Tislelizumab as the active substance and it is given by 200 mg administered as an intravenous (i.v.) infusion every 3 weeks.

Further information about the evaluation of Tevimbra’s benefits can be found in Tevimbra’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage https://www.ema.europa.eu/en/medicines/human/EPAR/tevimbra.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

Measures to minimise 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 authorised 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 (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Tevimbra, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

- Patient Card

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

II.A List of important risks and missing information

Important risks of Tevimbra are risks that need special risk management activities to further investigate or minimise 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 Tevimbra. 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 (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Immune-mediated adverse reactions
Important potential risks	Reproductive and developmental toxicity
Missing information	None

II.B Summary of important risks

Important identified risk: Immune-mediated adverse reactions	
Evidence for linking the risk to the medicine	Review of tislelizumab clinical trial data, post-marketing experience and literature regarding immune-mediated adverse reactions (including immune-mediated pneumonitis, immune-mediated hepatitis, immune-mediated skin adverse reaction, immune-mediated colitis, immune-mediated myositis/rhabdomyolysis, immune-mediated endocrinopathies, immune-mediated nephritis and renal dysfunction, immune-mediated myocarditis, immune-mediated nervous system disorder, immune-mediated pancreatitis, and other immune-mediated reactions) represent sufficient evidence of a causal association with tislelizumab exposure. **Immune-mediated pneumonitis** *Nonclinical data:* No treatment-related inflammation in lungs was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. *Clinical data:* The most common lung toxicity observed in patients receiving ICI treatment is pneumonitis. Reports of pneumonitis were documented in 2% to 4% of patients, with 1% to 2% of patients having grade ≥3 events, frequency of fatal pneumonitis in 0.2% of patients and discontinuation due to pneumonitis in 0.2% to 4% of patients. Patients with NSCLC were significantly more likely to experience any grade pneumonitis and grade 3 or higher pneumonitis compared with other tumor types. **Immune-mediated hepatitis** *Nonclinical data:* No treatment-related hepatic inflammation was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, or 60

	mg/kg (once every 2 weeks, 7 doses) for 13 weeks. *Clinical data:* Although infrequently observed, the occurrence of immune-mediated hepatitis is well established in patients treated with ICIs. These patients are typically asymptomatic, and diagnosis is made due to elevated liver enzymes such as ALT and/or AST, and occasionally hyperbilirubinemia. The median onset of transaminase elevation is approximately 6 to 14 weeks after starting ICI treatment, and the incidence of developing immune-mediated hepatitis in patients treated with ICIs is approximately 5. **Immune-mediated skin adverse reaction** *Nonclinical data:* No treatment-related skin rash was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. *Clinical data:* Skin AEs are among the most frequent AEs observed in patients treated with mAbs inhibiting either immune checkpoints CTLA4 (ipilimumab in 43% to 45% of the patients) or PD-1 (nivolumab and pembrolizumab in approximately 34% of the patients). However, serious skin AEs are rare and do not usually require dose reductions or treatment discontinuation. **Immune-mediated colitis** *Nonclinical data:* No treatment-related diarrhea or gastrointestinal tract inflammation was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. *Clinical data:* Diarrhea and colitis are more frequent with anti-cytotoxic T lymphocyte associated protein 4 (CTLA4) agents (e.g., ipilimumab) than with anti-PD-1 targeted agents including nivolumab or pembrolizumab, with grade 3 to 4 AEs occurring in 1% to 2% of cases (Haanen et al 2017). The presence of diarrhea in conjunction with abdominal pain, rectal bleeding, mucus in the stool, and fever should alert the clinician to the possibility of colitis, a potentially serious or even life-threatening gastrointestinal complication of ICI therapy. **Immune-mediated myositis/rhabdomyolysis:** *Nonclinical data:* No treatment-related inflammation in muscle was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. *Clinical data:* Immune-mediated myositis/rhabdomyolysis occur uncommonly in cancer patients treated with ICIs. Recognizing musculoskeletal imAEs in the oncology setting is challenging due to the broad range of potential presenting symptoms and the prevalence of musculoskeletal complaints in the general population. **Immune-mediated endocrinopathies (hypothyroidism, hyperthyroidism, thyroiditis, adrenal insufficiency, pituitary dysfunction, diabetes mellitus)** *Nonclinical data:* No treatment-related thyroid inflammation was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, or 60

	mg/kg (once every 2 weeks, 7 doses) for 13 weeks. *Clinical data:* Thyroid disease or abnormalities in thyroid function tests (primary hypothyroidism and thyroiditis) is one of the most common endocrine imAEs. Thyroid dysfunction (hypothyroidism, hyperthyroidism, and thyroiditis) was reported in 6 to 20% of patients in large Phase III clinical trials (Puzanov et al 2017). Pituitary dysfunction is a rare condition which occurs in 0.5-1% of patients treated with anti- PD-1/PD-L1 monotherapy and up to 10% with combination CTLA-4/PD-1 blockade. In contrast to thyroid disorders, most patients with pituitary dysfunction present with clinical symptoms commonly related to neuro-compression or more often, to secondary adrenal insufficiency including fatigue and nausea. Primary adrenal insufficiency is a rare complication of ICI therapy. Diabetes Mellitus following treatment with ICIs occurs in slightly less than 1% of patients; approximately 97% of all reported cases have arisen with anti-PD-1/PD-L1 monotherapy or combination treated patients. **Immune-mediated nephritis and renal dysfunction** *Nonclinical data:* No treatment-related inflammation in kidneys was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. Secondary renal changes were observed at 60 mg/kg due to immunogenicity against tislelizumab (anti-drug antibodies). *Clinical data:* In the published literature, renal immune-mediated AEs are considered rare. Most reports document isolated cases of interstitial nephritis with specific agents and regimens, such as anti-PD-1 monotherapy, and combination anti-CTLA-4/PD-1 treatment in melanoma. **Immune-mediated myocarditis** *Nonclinical data:* No treatment-related inflammation of the heart was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. *Clinical data:* Myocarditis and cardiac dysfunction due to ICIs are rare and the true incidence is unknown; current estimates suggest this incidence is less than 1% of patients. Cardiac immune-mediated AEs due to ICIs may present with nonspecific symptoms such as fatigue and weakness. However, more typical cardiac symptoms of chest pain, shortness of breath, pulmonary or lower extremity edema, palpitations, irregular heartbeat, rapid onset of heart failure symptoms or new heart block on electrocardiogram (ECG) can occur at any time, more frequently within the first few months of treatment and may lead to death. **Immune-mediated nervous system disorders** *Nonclinical data:* No treatment related inflammation in brain was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. *Clinical data:* Neurologic immune-related adverse events are uncommon with an overall incidence up to 6% with anti-PD-1 antibodies and include auto-

	immune encephalitis, myasthenic syndrome, Guillain-Barre syndrome. **Immune-mediated pancreatitis** *Nonclinical data:* No treatment related inflammation in pancreas was observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. *Clinical data:* Acute pancreatitis has been reported but is rare in cancer patients treated with ICIs; asymptomatic elevation of lipase and amylase are more common. **Other immune-mediated reactions** *Nonclinical data:* No other immune-mediated reactions were observed in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. *Clinical data:* Immune-related adverse events can affect any organ system, including hematological, ocular or rheumatological manifestations.
Risk factors and risk groups	Patients with a history of or ongoing autoimmune disease may be at a higher risk of developing imAEs and are generally excluded from the clinical development program for tislelizumab. There are currently no identified risk groups or risk factors that may predispose patients to developing immune-mediated adverse reactions after treatment with tislelizumab.
Risk minimisation measures	**Routine risk minimisation measures** SmPC Section 4.2 where guidelines for withholding or permanent discontinuation of treatment are provided. SmPC Section 4.4 where advice is provided regarding monitoring and management of immune-mediated adverse reactions. SmPC Section 4.8 where the adverse drug reactions (ADRs) of immune-mediated adverse reactions are listed. PL Section 2 and PL Section 4 where guidance on how to early identify signs and symptoms and seek medical attention is included. Legal status: Restricted medical prescription **Additional risk minimisation measures** Patient Card

Important Potential risk: Reproductive and developmental toxicity	
Evidence for linking the risk to the medicine	*Nonclinical data:* No treatment-related effects were observed in reproductive organs in cynomolgus monkeys following i.v. infusion at doses of 3, 10, 30, or 60 mg/kg (once every 2 weeks, 7 doses) for 13 weeks. However, not all animals in these studies were sexually mature. A literature-based assessment of effects on embryofetal toxicity demonstrated that the pharmacologically mediated blockade of PD-1/PD-L1 interaction in animal models can result in fetal loss. This is due to disruption of immune tolerance to the fetus as the

	PD-1/PD-L1 pathway plays a role in the maintenance of tolerance. *Clinical data:* A clinical study conducted by Meggyes et al 2019 further supports the animal model data and highlighted the potential importance of the PD-1/PD-L1 immune-checkpoint pathway in the induction of maternal tolerance during healthy pregnancy. The PD-1 binding to the abundantly expressed PD-L1 in tumors is analogous to the PD-1 binding to a highly-expressed PD-L1 at the utero-placental interface. The blockade of the PD-1/PD-L1 pathway in inducing fetal loss/abortion has been shown in murine models of allogeneic pregnancy. Therefore, the potential risks of administering a PD-1/PD-L1 inhibitor, including tislelizumab during pregnancy include increased rates of abortion or stillbirth. Based on the mechanism of action, the administration of tislelizumab during pregnancy could cause harm to the fetus.
Risk factors and risk groups	No relevant risk groups or risk factors have been identified.
Risk minimisation measures	**Routine risk minimisation measures** SmPC Section 4.6 where advice is provided regarding the need for women of child-bearing potential to avoid getting pregnant and for lactating women to avoid breastfeeding infants while taking tislelizumab and that, women of child-bearing potential should use effective contraception during treatment with tislelizumab and for 4 months after the last dose. SmPC Section 5.3 PL Section 2 where guidance on how to early identify signs and symptoms and seek medical attention is included. Legal status: Restricted medical prescription **Additional risk minimisation measures** None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Tevimbra.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Tevimbra.

Signature Page for VV-PVG-001958 v1.0

Approval with eSignature	Wassim Aldairy Drug Safety 03-Jun-2024 14:37:14 GMT+0000

Signature Page for VV-PVG-001958 v1.0