Swiss Summary of the Risk Management Plan (RMP)

Keytruda®

Active Substance: Pembrolizumab

RMP summary version 8.0 (Mar 2025)

Based on EU-RMP Version 45.0 (CHMP opinion 14-Nov-2024)

Marketing Authorisation Holder: MSD Merck Sharp & Dohme AG, Lucerne

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 Keytruda® 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, 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 Keytruda® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

MSD Merck Sharp & Dohme AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Keytruda®.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of risk management plan for pembrolizumab

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

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

I. The Medicine and What it is Used For

Melanoma

Pembrolizumab as monotherapy is indicated for the treatment of adults and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma.

Pembrolizumab as monotherapy is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection.

Non-small cell lung carcinoma (NSCLC)

Pembrolizumab in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults.

Pembrolizumab as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy.

Pembrolizumab as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.

Pembrolizumab, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.

Pembrolizumab, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults.

Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving pembrolizumab.

Malignant pleural mesothelioma (MPM)

Pembrolizumab, in combination with pemetrexed and platinum chemotherapy, is indicated for the first line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma.

Classical Hodgkin lymphoma (cHL)

Pembrolizumab as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin Lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

Urothelial carcinoma

Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy.

Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10.

Pembrolizumab, in combination with enfortumab vedotin is indicated for the first-line treatment of unresectable or metastatic urothelial carcinoma in adults.

Head and neck squamous cell carcinoma (HNSCC)

Pembrolizumab, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1.

Pembrolizumab as monotherapy is indicated for the treatment of recurrent or metastatic HNSCC in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy.

Renal cell carcinoma (RCC)

Pembrolizumab, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) in adults.

Pembrolizumab, in combination with lenvatinib, is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) in adults.

Pembrolizumab as monotherapy is indicated for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers

Colorectal cancer (CRC)

Pembrolizumab as monotherapy is indicated for adults with MSI-H or dMMR colorectal cancer in the following settings:

- first-line treatment of metastatic colorectal cancer;
- treatment of unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy.

Non-colorectal cancers

Pembrolizumab as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:

- advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation;
- unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

Oesophageal carcinoma

Pembrolizumab, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PD-L1 with a CPS ≥ 10

Triple negative breast cancer (TNBC)

Pembrolizumab, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer (TNBC) at high risk of recurrence.

Pembrolizumab, in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) in adults whose tumors express PD-L1 with a CPS ≥10 and who have not received prior chemotherapy for metastatic disease.

Endometrial carcinoma (EC)[MS1]

Pembrolizumab, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults who are candidates for systemic therapy.

Pembrolizumab, in combination with lenvatinib, is indicated for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.

Cervical cancer

Pembrolizumab, in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy), is indicated for the treatment of FIGO 2014 Stage III - IVA locally advanced cervical cancer in adults who have not received prior definitive therapy.

Pembrolizumab, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1.

Gastric or gastro-oesophageal junction adenocarcinoma

Pembrolizumab, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

Pembrolizumab, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

Biliary tract carcinoma (BTC)

Pembrolizumab, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.

It contains 100 mg liquid pembrolizumab in a 10 mL single-use vial as the active substance and it is given by intravenous infusion.

The Recommended Dose of Pembrolizumab is:

- 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes.

Further information about the evaluation of pembrolizumab's benefits can be found in pembrolizumab's European Public Assessment Report (EPAR), including in its plain-language summary, available on the EMA website, under the medicine's webpage link to product's EPAR summary landing page on the EMA webpage at the following link:

https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of pembrolizumab, together with measures to minimise such risks and the proposed studies for learning more about pembrolizumab'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 pembrolizumab, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below. 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*. If important information that may affect the safe use of pembrolizumab is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of pembrolizumab 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 pembrolizumab. 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).

Pembrolizumab has been on the market since July of 2015. Risk minimization activities recommending specific clinical measures to address the risks have become fully integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines. The identified risks in the EU RMP are: Immune-mediated adverse reactions.

The potential risks in the EU RMP include: an increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab and Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT).

Table II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Immune-mediated adverse reactions
Important potential risks	For hematologic malignancies: increased risk of severe complications of allogeneic stem cell transplantation (SCT) in patients who have previously received pembrolizumab Graft versus host disease (GVHD) after pembrolizumab administration in patients with a history of allogeneic stem cell transplant (SCT)

Table II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Missing information	None

II.B Summary of Important Risks

Table II.B.1: Important Identified Risk: Immune-Mediated Adverse Reactions

Evidence for linking the risk to the medicine	Review of pembrolizumab clinical trial data, post-marketing experience and literature regarding immune-mediated adverse reactions represent sufficient evidence of a causal association with pembrolizumab exposure. pembrolizumab KN001 Database Cutoff Date: 18APR2014 pembrolizumab KN001 Database Cutoff Date for Lung: 23JAN2015 pembrolizumab KN002 Database Cutoff Date: 28FEB2015 pembrolizumab KN006 Database Cutoff Date: 03MAR2015 pembrolizumab KN010 Database Cutoff Date: 30SEP2015 pembrolizumab KN013 Database Cutoff Date for Hodgkin Lymphoma: 28SEP2018 pembrolizumab KN024 Database Cutoff Date: 10JUL2017 pembrolizumab KN087 Database Cutoff Date: 21MAR2019 pembrolizumab KN045 Database Cutoff Date: 07SEP2016 pembrolizumab KN052 Database Cutoff Date: 01SEP2016 pembrolizumab KN021 Database Cutoff Date Cohort A: 07NOV2016, Cohort G/C: 31MAY2017 pembrolizumab KN189 Database Cutoff Date: 08NOV2017 pembrolizumab KN040 Database Cutoff Date: 15MAY2017 pembrolizumab KN012 Database Cutoff Date: 26APR2016 pembrolizumab KN055 Database Cutoff Date: 22APR2016 pembrolizumab KN054 Database Cutoff Date: 02OCT2017 pembrolizumab KN407 Database Cutoff Date: 03APR2018 pembrolizumab KN426 Database Cutoff Date: 24AUG2018 pembrolizumab KN048 Database Cutoff Date: 13JUN2018 pembrolizumab KN042 Database Cutoff Date: 26FEB2018 pembrolizumab KN177 Database Cutoff Date: 19FEB2020 pembrolizumab KN204 Database Cutoff Date: 16JAN2020 pembrolizumab KN590 Database Cutoff Date: 02JUL2020 pembrolizumab KN355 Database Cutoff Date: 11DEC2019 pembrolizumab KN581 Database Cutoff Date: 28AUG2020 pembrolizumab KN146 Database Cutoff Date: 18AUG2020 pembrolizumab KN775 Database Cutoff Date: 26OCT2020 pembrolizumab KN564 Database Cutoff Date: 14DEC2020 pembrolizumab KN158 Database Cutoff Date Cohort K: 05OCT2020 pembrolizumab KN164 Database Cutoff Date Cohorts A and B: 09SEP2019 pembrolizumab KN826 Database Cutoff Date: 03MAY2021 pembrolizumab KN522 Database Cutoff Date: 23MAR2021 pembrolizumab KN716 Database Cutoff Date: 04DEC2020 pembrolizumab KN811 Database Cutoff Date: 25MAY2022 pembrolizumab KN091 Database Cutoff Date: 20SEP2021 pembrolizumab KN859 Database Cutoff Date: 03OCT2022 pembrolizumab KN966 Database Cutoff Date: 15DEC2022 pembrolizumab KN671 Database Cutoff Date: 29JUL2022 pembrolizumab KN869 Database Cutoff Date: 13MAR2023 pembrolizumab KNA39 Database Cutoff Date: 08AUG2023

Table II.B.1: Important Identified Risk: Immune-Mediated Adverse Reactions

	pembrolizumab KN868 Database Cutoff Date: 16Dec2022 for dMMR participants and 06Dec2022 for pMMR participants pembrolizumab KNA18 Database Cutoff Date: 09JAN2023 pembrolizumab KN483 Database Cutoff Date: 16SEP2022 pembrolizumab KNA17 Database Cutoff Date: 21SEP2022
Risk factors and risk groups	**Pneumonitis** Patients with a history of non-infectious pneumonitis that required steroids or current pneumonitis were excluded from the clinical trials. These patients are considered to be a risk group for the development of pneumonitis; in the interim analysis of the KN001 NSCLC cohort, possible risk factors identified that might predispose subjects to pneumonitis were a documented history of prior thoracic radiation to the chest (≥30Gy). According to the literature, risk factors for interstitial lung disease may include occupational exposure to toxins, chest irradiation, some chemotherapies, smoking and advanced age. **Colitis** No specific risk factors for colitis and diarrhea associated with pembrolizumab were identified. **Hepatitis** Patients with moderate to severe liver dysfunction were excluded from clinical trials. No analysis of specific risk factors for immune-mediated hepatitis associated with pembrolizumab has been undertaken. **Nephritis** Patients with severe renal dysfunction were excluded from clinical trials. No specific risk factors for nephritis associated with pembrolizumab have been identified. **Endocrinopathies** No specific risk factors for endocrinopathies associated with pembrolizumab have been identified.

Table II.B.1: Important Identified Risk: Immune-Mediated Adverse Reactions

Risk minimisation measures	Routine risk minimisation measures: • The risk of the immune-mediated adverse reactions associated with the use of pembrolizumab is described in the SmPC, Section 4.2, 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk. Additional risk minimisation measures: • Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Safety monitoring in all ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types.

Table II.B.2: Important Potential Risk: For Hematologic Malignancies: Increased Risk of Severe Complications of Allogeneic Stem Cell Transplantation (SCT) in Patients Who Have Previously Received Pembrolizumab

Evidence for linking the risk to the medicine	Review of pembrolizumab literature regarding increased risk of severe complications of allogeneic stem cell transplantation in patients who have previously received pembrolizumab represents scientific evidence of a possible causal association with pembrolizumab exposure.
Risk factors and risk groups	Patients with hematologic malignancies undergoing allogeneic SCT who were previously treated with a PD-1 inhibitor.
Risk minimisation measures	Routine risk Minimisation measures: • For Hematologic malignancies: the increased risk of severe complications of allogeneic SCT in patients who have previously received pembrolizumab is described in the SmPC, Section 4.4, 4.8 and appropriate advice is provided to the prescriber to minimize the risk.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Safety monitoring in the ongoing HL trial (KN204)

Table II.B.3: Important Potential Risk: Graft Versus Host Disease (GVHD) After Pembrolizumab Administration in Patients With a History of Allogeneic Stem Cell Transplant (SCT)

Evidence for linking the risk to the medicine	Published literature Postmarketing data
Risk factors and risk groups	Patients with a history of allogeneic SCT treated with a PD-1 inhibitor.
Risk minimisation measures	Routine risk Minimisation measures: • GVHD after pembrolizumab administration in patients with a history of allogeneic SCT is described in the SmPC, Section 4.4 and appropriate advice is provided to the prescriber to minimize the risk.
Additional pharmacovigilance activities	Routine pharmacovigilance activities Additional pharmacovigilance including: • Safety monitoring in all other ongoing MAH-sponsored clinical trials for pembrolizumab in various tumor types

II.C Post-Authorisation Development Plan

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

The following studies are conditions of the marketing authorisation:

Table II.C.1.1: Studies Which are Conditions of the Marketing Authorisation

Study Title	Objectives
Efficacy studies which are conditions of the marketing authorisation	
A randomized, placebo-controlled, parallel-group, crossover/rechallenge, multi-center study of adjuvant pembrolizumab in participants 12 years of age and older with resected Stage IIB and IIC cutaneous melanoma (KN716) (on-going)	The value of biomarkers to predict the efficacy of pembrolizumab should be further explored, specifically: Additional biomarkers other than PD-L1 expression status by Immunohistochemistry (IHC) (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy should be investigated together with more information regarding the pattern of expression of PD L1 obtained in the resected Stage II melanoma adjuvant study (KN716): • Genomic analyses using whole exome sequencing and/or RNAseq (e.g. Nanostring RNA gene signature) • IHC staining for PD-L2 • Data on RNA and proteomic serum profiling
A Phase III, Randomized, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma (KN204) (on-going)	To compare overall survival (OS), progression free survival (PFS) and objective response rate (ORR) of pembrolizumab when compared to Brentuximab Vedotin in subjects with relapsed or refractory cHL and to examine the safety and tolerability between treatment groups.

Table II.C.1.1: Studies Which are Conditions of the Marketing Authorisation

Study Title	Objectives
Adjuvant immunotherapy with anti-PD-1 monoclonal antibody Pembrolizumab (MK-3475) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 trial of the EORTC Melanoma Group (KN054) (on-going)	To prospectively assess whether post-operative adjuvant therapy with pembrolizumab improves recurrence-free survival (RFS) as compared to placebo in high-risk patients with complete resection of Stage IIIA (> 1 mm metastasis), IIIB and IIIC melanoma. To prospectively assess whether in the subgroup of patients with PD-L1-positive tumor expression, pembrolizumab improves recurrence-free survival as compared to placebo (primary endpoint); distant metastasis free survival (DMFS) and overall survival (OS) in all-subjects and subjects with PD-L1-positive tumors (secondary endpoints for final study report).
A Phase II study of pembrolizumab (MK-3475) in previously treated participants with advanced solid tumors (KN158) (on-going)	To evaluate the antitumor activity of pembrolizumab in participants with MSI-H/dMMR gastric, biliary and small intestine cancer.
A randomized, placebo-controlled, parallel-group, crossover/rechallenge, multi-center study of adjuvant pembrolizumab in participants 12 years of age and older with resected Stage IIB or IIC cutaneous melanoma (KN716) (on-going)	To compare RFS, DMFS and OS between pembrolizumab and placebo in patients with resected Stage IIB or IIC melanoma.
A randomized, Phase 3 trial with pembrolizumab versus placebo for patients with early stage NSCLC after resection and completion of standard adjuvant therapy (KN091) (on-going)	To compare OS between pembrolizumab and placebo in patients with early stage NSCLC after resection and completion of standard adjuvant therapy To assess data on treatment post-progression, and particularly on the uptake and activity of anti-PD(L)1 in patients previously treated with adjuvant pembrolizumab

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for pembrolizumab.