PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR ATEZOLIZUMAB (TECENTRIQ)

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

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

This summary of the RMP for Tecentriq 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 Tecentriq RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Monotherapy

Tecentriq as monotherapy is authorized for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC)

- after prior platinum-containing chemotherapy, or
- who are considered cisplatin ineligible, and whose tumors have a PD-L1 expression ≥ 5%.

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Patients with epidermal growth factor receptor (EGFR)-activating mutations or anaplastic lymphoma kinase (ALK)-positive tumor mutations should also have received targeted therapy before receiving Tecentriq (see SmPC for the full indication). It contains Atezolizumab as the active substance and it is given by intravenous infusion over 60 minutes every 3 weeks.

Tecentriq as monotherapy for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a PD-L1 expression ≥50% tumour cells (TC) or ≥10% tumour-infiltrating immune cells (IC) and who do not have EGFR mutant or ALK-positive NSCLC.

Combination Therapy

Tecentriq, in combination with bevacizumab, is indicated for the treatment of adult patients with unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

Tecentriq, in combination with nab-paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC.

Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. Patients with EGFR activating mutations or ALK-positive tumour mutations should also have received targeted therapy, if clinically indicated, prior to receiving Tecentriq.

Tecentriq, in combination with nab-paclitaxel, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors have PD-L1 expression $\geq$ 1% and who have not received prior chemotherapy for metastatic disease.

Tecentriq, in combination with carboplatin and etoposide, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

Further information about the evaluation of Tecentriq benefits can be found in Tecentriq 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 MINIMISE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Tecentriq, together with measures to minimize such risks and the proposed studies for learning more about Tecentriq 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 (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition, information about adverse events is collected continuously and regularly analyzed: 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 Tecentriq is not yet available, it is listed under 'missing Information' below.

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of Tecentriq 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 Tecentriq. 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-related hepatitis Immune-related pneumonitis Immune-related colitis Immune-related pancreatitis Immune-related endocrinopathies (Diabetes Mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, and hypophysitis) Immune-related neuropathies (Guillain-Barré syndrome, myasthenic syndrome / myasthenia gravis) Immune related meningoencephalitis Immune-related myocarditis Infusion-related reactions Immune-related nephritis Immune-related myositis
Important potential risks	Anti-drug antibodies Embryo-fetal toxicity
Missing information	Long term use Concomitant or sequential use of atezolizumab with intra-vesical bacillus Calmette-Guérin vaccine for the treatment of urothelial carcinoma

II.B SUMMARY OF IMPORTANT RISKS

Important identified risk: Immune-Related Hepatitis	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	There are no identified risk factors for the development of immune-related hepatitis in atezolizumab treated patients.
Risk minimization measures	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 –Undesirable effects Relevant information for patient in PIL **Additional risk minimization measures:** Patient alert cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Immune-Related Pneumonitis	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	General factors that may be associated with an increased risk of drug-induced ILD include: older age, male sex, pre-existing lung disease, smoking, prior radiation therapy, prior or concomitant treatment with medications with known pulmonary toxicity (e.g., some antimicrobial, anti-inflammatory and cardiovascular agents, biologics, and chemotherapeutics), inflammatory conditions (e.g., rheumatoid arthritis and inflammatory bowel disease). The underlying malignant disease itself may also increase the risk of pneumonitis and be a confounder of diagnosis (Barber et al. 2011; Schwaiblmair et al. 2012). There are currently no known risk factors that may predispose individual patients to develop immune-related pneumonitis following treatment with atezolizumab.
Risk minimization measures	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 – Undesirable effects Relevant information for patient in PIL **Additional risk minimization measures:** Patient alert cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Immune-Related Colitis	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	There are currently no known risk factors that may predispose individual patients to develop immune-related colitis following treatment with atezolizumab.
Risk minimization measures	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 – Undesirable effects Relevant information for patient in PIL **Additional risk minimization measures:** Patient alert cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Immune-Related Pancreatitis	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	Female sex, younger age, and pre-existing inflammatory bowel disease may be associated with an increased risk of drug-induced pancreatitis (Nitsche et al. 2012, Vinklerova et al. 2010). There are currently no known risk factors that may predispose individual patients to develop immune-related pancreatitis following treatment with atezolizumab.
Risk minimization measures	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 – Undesirable effects Relevant information for patient in PIL **Additional risk minimization measures:** Patient alert cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Immune-Related Endocrinopathies (Diabetes Mellitus, Hypothyroidism, Hyperthyroidism, Adrenal Insufficiency, and Hypophysitis)	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	An Italian study of adults between age 30 and 49 years found that the risk of type 1 diabetes was almost two times higher in males compared with females (rate ratio [RR] 1.70 [95% CI 1.21 – 2.38]) (Bruno et al. 2005). There are currently no known risk factors that may predispose individual patients to develop immune-related diabetes following treatment with atezolizumab. There are no known risk factors associated with the development of immune-related hypo- or hyperthyroidism, adrenal insufficiency, or hypophysitis in individual atezolizumab treated patients.
Risk minimization measures	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 – Undesirable effects Relevant information for patient in PIL **Additional risk minimization measures:** Patient alert cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Immune-Related Neuropathies (Guillain-Barré Syndrome and Myasthenia Gravis/Myasthenic Syndrome)	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	There are no known risk factors associated with the development of immune-related neuropathies in atezolizumab - treated patients.
Risk minimization measures	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 – Undesirable effects Relevant information for patient in PIL **Additional risk minimization measures:** Patient alert cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Immune-Related Meningoencephalitis	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	There are no known risk factors associated with the development of immune-related meningoencephalitis in atezolizumab-treated patients.
Risk minimization measures	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 – Undesirable effects Relevant information for patient in PIL **Additional risk minimization measures:** Patient alert cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Infusion-Related Reactions	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	Treatment with monoclonal antibodies is associated with an increased risk for infusion-related reactions. (Keating et al. 2014; Thompson et al. 2014). There are no known risk factors associated with the development of IRRs in atezolizumab-treated patients.
Risk minimization measures	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 – Undesirable effects Relevant information for patient in PIL **Additional risk minimization measures:** Patient alert cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Immune-Related Myocarditis	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	There are no known risk factors associated with the development of immune-related myocarditis in atezolizumab-treated patients
Risk minimization measures	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 –Undesirable effects Relevant information for patient in PIL **Additional risk minimization measures:** Patient alert cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Immune-Related Nephritis	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	There are no known risk factors associated with the development of immune-related nephritis in atezolizumab-treated patients
Risk minimization measures	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 –Undesirable effects Relevant information for patient in PIL **Additional risk minimization measures:** Patient alert cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk: Immune-Related Myositis	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	There are no known risk factors associated with the development of immune-related myositis in atezolizumab-treated patients
Risk minimization measures	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.2 Posology and method of administration Section 4.4 Special Warnings and Precautions for Use Section 4.8 –Undesirable effects Relevant information for patient in PIL **Additional risk minimization measures:** Patient alert cards
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important potential risk: Anti-drug antibodies	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	Risk factors for the development of ADAs are currently unknown.
Risk minimization measures	**Routine risk minimization measures**: Proposed measures are described in the E.U. SmPC under the following sections: Section 4.8 – Undesirable effects **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important potential risk: Embryo-fetal toxicity	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	The at-risk group for experiencing atezolizumab-related embryo-fetal toxicity includes female patients of child-bearing potential and developing fetuses who are exposed to atezolizumab during gestation.
Risk minimization measures	**Routine risk minimization measures**: Proposed measures are described in the E.U. SmPC under the following sections: Section 4.6 Fertility, pregnancy and lactation Section 5.3 Preclinical safety data **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Missing Information: Long-term use	
Risk minimization measures	**Routine risk minimization measures:** Proposed text in E.U. SmPC None **Additional risk minimization measures:** Not applicable
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Studies MO29983 and MO39171

Missing Information: Concomitant or sequential use of atezolizumab with intra-vesical BCG vaccine for the treatment of urothelial carcinoma	
Risk minimization measures	**Routine risk minimization measures:** Proposed measures are described in the E.U. SmPC under the following sections: Section 4.4 Special Warnings and Precautions for Use: Includes language that patients who were administered a live attenuated vaccine with 28 days prior to enrolment were excluded from clinical trials **Additional risk minimization measures:** Not applicable
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study WO29635

II.C POST-AUTHORISATION DEVELOPMENT PLAN

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

The following studies are conditions of the marketing authorization:

GO29293 (IMvigor210): A Phase II, multicenter, single-arm study of atezolizumab in patients with locally advanced or metastatic urothelial bladder cancer.

Purpose of the study:

- To evaluate efficacy of atezolizumab in patients with locally advanced or metastatic UC as measured by ORR (primary objective), PFS, DOR, OS and 1-year OS
- To evaluate safety and tolerability of atezolizumab

- To evaluate the incidence of ADAs against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy

WO30070 (IMvigor130): A phase III, multicenter, randomized, placebo-controlled study of atezolizumab (anti-PD-L1 antibody) as monotherapy and in combination with platinum-based chemotherapy in patients with untreated locally advanced or metastatic urothelial carcinoma

Purpose of the study:

- to evaluate the efficacy of atezolizumab plus platinum-based chemotherapy compared with placebo plus platinum-based chemotherapy
- to evaluate the efficacy of atezolizumab given as either monotherapy or in combination with platinum-based chemotherapy compared with placebo in combination with platinum-based chemotherapy
- to evaluate the efficacy of atezolizumab monotherapy compared with placebo plus platinum-based chemotherapy on the basis of OS
- to evaluate the safety and tolerability of atezolizumab given as either monotherapy or in combination with platinum-based chemotherapy compared with placebo plus platinum-based chemotherapy

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

WO29635: A Phase IB/II, Open-Label Study of the Safety and Pharmacology of Atezolizumab Administered with or without Bacille Calmette-Guérin in Patients with High Risk Non Muscle-Invasive Bladder Cancer

Purpose of study:

- To evaluate the safety and tolerability of atezolizumab as a single agent and in combination with BCG.
- To identify the DLTs and to determine the MTD or tolerability at the MAD of BCG in combination with atezolizumab

MO39171: Single-Arm Long-Term Safety and Efficacy Study of atezolizumab in previously treated NSCLC Patients**.**

Purpose of study:

- To evaluate the long-term safety of atezolizumab on the bases of the following endpoints: The incidence of all serious adverse events (SAEs) related to atezolizumab treatment and the incidence of serious and non-serious immune-related adverse events (irAEs) related to atezolizumab treatment.

MO29983: An Open-Label, Single Arm, Multicenter, Safety Study of atezolizumab in Locally Advanced or Metastatic Urothelial or Non-Urothelial Carcinoma of the Urinary Tract**.**

Purpose of study:

- To evaluate the safety of atezolizumab based on the following endpoints: Nature, severity, duration, frequency and timing of adverse events (AEs) and changes in vital signs, physical findings, and clinical laboratory results during and following atezolizumab administration.

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