Swiss Summary of the Risk Management Plan (RMP) for Mobocertinib (EXKIVITY)

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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 risk as well as to prevent or minimize them.

The RMP summary of EXKIVITY 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 authorization.

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

Summary of risk management plan for EXKIVITY (Mobocertinib)

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

EXKIVITY's summary of product information (PI) gives essential information to healthcare professionals and patients on how EXKIVITY should be used.

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

I. The medicine and what it is used for

EXKIVITY is authorised as monotherapy for the treatment of adult patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutation-positive unresectable or metastatic non-small cell lung cancer (NSCLC), whose disease has progressed on or after platinum-containing chemotherapy (see PI for the full indication). It contains mobocertinib as the active substance and it is given by oral route at 160 mg (free base equivalence) once daily (QD) in hard gelatin capsule form.

Further information about the evaluation of EXKIVITY can be found in the Swiss- PAR, which includes a lay-language summary, and is available on the Swiss Agency for Therapeutic products (Swissmedic) website, under the medicine's webpage:

https://www.swissmedic.ch/dam/swissmedic/en/dokumente/zulassung/swisspar/68147-exkivity-01-swisspar-20220803.pdf.download.pdf/SwissPAR_Exkivity.pdf.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of EXKIVITY, together with measures to minimise such risks and the proposed studies for learning more about EXKIVITY'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 PI 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 addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (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 EXKIVITY is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of EXKIVITY 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 EXKIVITY. 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	• Pneumonitis/Interstitial Lung Disease • Ventricular arrhythmias, including Torsades de pointes, due to QTc interval prolongation • Cardiac failure
Important potential risks	• Reproductive and developmental toxicity
Missing information	• Long-term use

II.B Summary of important risks

Pneumonitis/Interstitial Lung Disease	
Evidence for linking the risk to the medicine	Pneumonitis/Interstitial Lung Disease is known to be a class effect of EGFR Tyrosine Kinase Inhibitors (TKIs) and a potential causal association has been observed with mobocertinib in the clinical trial.
Risk factors and risk groups	Male sex, a history of smoking, pre-existing pulmonary fibrosis, prior radiotherapy, Anti-PD-1 monoclonal antibodies are the possible risk factors for TKI induced pneumonitis/ILD.
Risk minimization measures	**Routine risk minimisation measures:** Prescribers are informed on early recognition / diagnosis and management of pneumonitis/ILD and recommendation on the therapy discontinuation approach is provided if pneumonitis/ILD occurs. Patients/Caregivers are informed of sign/symptoms of pneumonitis/ILD and advised to contact to HCPs immediately in case of sign/symptoms observed. **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study TAK-788-3001.

Ventricular arrhythmias, including Torsades de pointes, due to QTc interval prolongation	
Evidence for linking the risk to the medicine	On the basis of clinical study results, there is reasonable possibility that the relationship between exposure to mobocertinib and development of QTc interval prolongation is causal. Heart ratecorrected QT interval prolongation has been observed with other EGFR TKIs in the class.
Risk factors and risk groups	Pre-existing cardiac disease, hypertension, diabetes, and hyperlipidaemia are major contributors while other factors like family history, activity level, smoking, elder age, gender, exposure to medications which alters cardiac conduction and alcohol intake status.

Risk minimization measures	**Routine risk minimisation measures:** Prescribers are advised on routinely monitor patients for QTc interval prolongation and electrolyte imbalances. The dose modification including dose reduction, treatment interruption or discontinuation) approach is recommended. Patients/Caregivers are informed of sign/symptoms and advised to contact to HCPs immediately if observed. **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study TAK-788-3001.

Cardiac failure	
Evidence for linking the risk to the medicine	On the basis of clinical study results, there is sufficient evidence demonstrating potential causal association. Cardiac failure has been observed with other EGFR TKIs in the class.
Risk factors and risk groups	Pre-existing cardiac disease, hypertension, diabetes, and hyperlipidaemia are major diagnoses that can contribute to the development of heart failure in patients using the TKIs.
Risk minimization measures	**Routine risk minimisation measures:** Prescribers are advised on cardiac function monitoring of patients and therapy discontinuation approach is recommended if patients develops cardiac failure. Patients/Caregivers are informed of sign/symptoms and advised to contact to HCPs immediately if observed. **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study TAK-788-3001.

Reproductive and developmental toxicity	
Evidence for linking the risk to the medicine	Reproductive and developmental toxicity is a potential risk based on preclinical studies and is known to be associated with EGFR TKIs.
Risk factors and risk groups	Female patients of reproductive potential and male patients who are sexually active with women of childbearing potential.
Risk minimization measures	**Routine risk minimisation measures:** Prescribers are informed to emphasise to the patients on the need of adequate contraception during and at least 1 month after

	mobocertinib therapy and informed of potential hazards to foetus in case of pregnancy exposure to mobocertinib. The patients are advised to discuss on the use of the effective method of contraception during and after stopping mobocertinib therapy with treating physicians. **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Missing information: Long-term use	
Risk minimization measures	**Routine risk minimisation measures:** None. **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study TAK-788-3001.

II.C. Post-authorisation development plan

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

Study short name: TAK-788-3001

Purpose of study: A Randomized Phase 3 Multicenter Open-label Study to Compare the Efficacy of TAK 788 as First-line Treatment Versus Platinum-Based Chemotherapy in Patients With Non–Small Cell Lung Cancer With EGFR Exon 20 Insertion Mutations. The study was designed to confirm the clinical benefit observed initially from non-controlled study. In addition, the safety data from this study will be used to further characterize the important identified risks of ventricular arrhythmias, including Torsades de pointes, due to QTc interval prolongation, cardiac failure, pneumonitis/interstitial lung disease and missing information of long-term use.

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

There are no studies required for Mobocertinib.