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Swiss Summary of the Risk Management Plan for Trikafta® (elexacaftor/tezacaftor/ivacaftor)

Version 6.0 (dated 12 June 2023)

Based on the EU-RMP Version 6.1

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 Trikafta® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary may 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 Trikafta® in Switzerland, is the "Arzneimittelinformation/ Information sur le medicament" (see www.swissmedicinfo.ch), approved and authorised by Swissmedic.

Vertex Pharmaceuticals (CH) GmbH is fully responsible for the accuracy and correctness of the content of the published RMP summary of Trikafta®.

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SUMMARY OF RISK MANAGEMENT PLAN FOR TRIKAFTA (ELEXACAFTOR IN COMBINATION WITH TEZACAFTOR AND IVACAFTOR)

This is a summary of the risk management plan (RMP) for Trikafta (elexacaftor/tezacaftor/ivacaftor [ELX/TEZ/IVA]) in Switzerland. The RMP details important risks of Trikafta, how these risks can be minimised, and how more information will be obtained about Trikafta's risks and uncertainties (missing information).

Trikafta's product information and its package information leaflet give essential information to healthcare professionals and patients on how Trikafta should be used.

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

I. The medicine and what it is used for

Trikafta is authorised for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation in the CF transmembrane conductance regulator (*CFTR)* gene (see Product Information for the full indication). It contains elexacaftor in combination with tezacaftor and ivacaftor as the active substances in the morning dose and ivacaftor as the active substance in the evening dose. Trikafta is given orally.

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

Important risks of Trikafta, together with measures to minimise such risks and the proposed studies for learning more about Trikafta'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 product information 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.

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

II.A List of important risks and missing information

Important risks of Trikafta are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Trikafta. 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	• Susceptibility for influenza virus infections • Hepatotoxicity
Important potential risks	• Cataract
Missing information	• Use in pregnant and lactating women • Long-term safety • Use in patients with moderate or severe hepatic impairment • Use in children aged 6 to 11 years

II.B Summary of important risks

Susceptibility for influenza virus infections (Important identified risk)	
Evidence for linking the risk to the medicine	In the 24-week, placebo-controlled Phase 3 study in CF subjects 12 years of age and older (Study 102), a higher incidence of influenza AEs was reported in the ELX/TEZ/IVA group compared to the placebo group. In the ELX/TEZ/IVA group, all AEs of influenza were mild or moderate in severity and most were non-serious. All subjects continued ELX/TEZ/IVA dosing or resumed treatment after an interruption. In the open-label extension Study 105, the rate of influenza AEs during extended ELX/TEZ/IVA treatment was lower than the rate in the ELX/TEZ/IVA group in Study 102, and similar to the rate in the placebo group in Study 102. The influenza data in subjects aged 6 to 11 years (Study 106) was consistent with those aged 12 years and older. Based on the overall safety experience with ELX/TEZ/IVA, an association between treatment and the susceptibility for influenza cannot be completely excluded.
Risk factors and risk groups	Patients who are hospitalised frequently or for long-term durations are at a greater risk for contracting influenza from other infected individuals. Risk factors for influenza-related complications include common CF comorbidities (e.g., chronic lung disease, asthma) and a compromised immune system.
Risk minimisation measures	PI “Undesirable effects” PL “Possible side effects” Prescription only
Additional pharmacovigilance activities	• Post-authorisation safety study • Open-label extension study (Study 107) See Section II.C of this summary for an overview of the post-authorisation development plan.
Hepatotoxicity (Important identified risk)	
Evidence for linking the risk to the medicine	In the 24-week, placebo-controlled, Phase 3 study in CF subjects 12 years of age and older (Study 102), the incidence of elevated transaminase events (AEs or ALT/AST laboratory elevations >3 × ULN) was higher in the group of subjects treated with ELX/TEZ/IVA than in the group of subjects receiving placebo. LFT elevations were also seen in other clinical studies with ELX/TEZ/IVA, including the open-label extension study (Study 105). Considering the high prevalence of LFT elevations in pediatric CF patients, LFT data observed in subjects aged 6 to 11 years (Study 106) were generally consistent with the safety profile established in subjects aged 12 years and older. Elevated transaminases with ELX/TEZ/IVA treatment were generally transient and resolved without long-term effects. Very high levels of transaminase elevations or transaminase elevations with concurrent total bilirubin elevation may be a sign of liver injury which could become permanent or be life-threatening. In addition, postmarketing reports of drug-induced liver injury have been received, including cases of liver injury

	characterized by concurrent elevations of transaminases and bilirubin, and one case of liver failure leading to transplantation in a patient with pre-existing cirrhosis and portal hypertension. An association with Trikafta (ELX/TEZ/IVA) treatment cannot be excluded in these cases. A causal association between treatment and hepatotoxicity cannot be excluded.
Risk factors and risk groups	Generally known risk factors for increases in transaminases include concurrent acute and chronic infections or illnesses (e.g., pulmonary exacerbation, flu-like illness, viral hepatitis), comorbidities (e.g., CF liver disease), and use of concomitant drugs (e.g., acetaminophen, antibiotics) or substances (alcohol) known to be associated with liver enzyme elevations.
Risk minimisation measures	PI "Warnings and precautions" and "Undesirable effects" PI "Warnings and precautions" where liver damage and worsening of liver function in people with severe liver disease is discussed and advice is given on monitoring LFTs PL "When is caution required when taking Trikafta" and "Possible side effects" Prescription only
Additional pharmacovigilance activities	• Post-authorisation safety study • Open-label extension study (Study 107) See Section II.C of this summary for an overview of the post-authorisation development plan.
Cataract (Important potential risk)	
Evidence for linking the risk to the medicine	Cataracts (lens opacities) considered related to IVA treatment were seen during studies in newborn rats but were not observed in older animals or in longer duration animal studies. Given developmental differences between rats and humans, it is unlikely that the cataract finding is relevant to humans 6 years of age and older. Non-congenital cataracts without impact on vision have been reported in paediatric subjects treated with IVA-containing regimens during clinical studies and post-authorisation surveillance, but the relationship of these events to treatment is uncertain due to the presence of other possible causes.
Risk factors and risk groups	Risk factors for cataracts include aging, trauma, UV light and radiation exposure, diabetes mellitus, intraocular inflammation, and corticosteroid use.
Risk minimisation measures	PI "Warnings and precautions" and "Preclinical data" PI "Warnings and precautions" where advice is given on recommended ophthamological examinations. PL "What is caution required when taking Trikafta" Prescription only
Additional pharmacovigilance activities	• Open-label extension study (Study 107) See Section II.C this summary for an overview of the post-authorisation development plan.
Use in pregnant and lactating women (Missing information)	
Risk minimisation measures	PI "Pregnancy, lactation" and "Preclinical data" PI "Pregnancy, lactation" where advice is given regarding use during pregnancy and breastfeeding. PL "Can Trikafta be taken during pregnancy and breastfeeding?" Prescription only
Additional pharmacovigilance activities	• Post-authorisation safety study See Section II.C of this summary for an overview of the post-authorisation development plan.

Long-term safety (Missing information)	
Risk minimisation measures	PI "Undesirable effects" and "Pharmacodynamic properties" Prescription only
Additional pharmacovigilance activities	• Post-authorisation safety study • Open-label extension study (Study 107) See Section II.C of this summary for an overview of the post-authorisation development plan.
Use in patients with moderate or severe hepatic impairment (Missing information)	
Risk minimisation measures	PI "Dosage/Administration" and "Pharmacokinetic properties" PI "Dosage/Administration" where recommendations regarding use in patients with hepatic impairment are provided. PL "How to take Trikafta?" and "When is caution required when taking Trikafta?" PL "How to take Trikafta?" and "When is caution required when taking Trikafta?" where advice to speak with a healthcare professional before use in patients with liver problems is provided. Prescription only
Additional pharmacovigilance activities	• Post-authorisation safety study See Section II.C of this summary for an overview of the post-authorisation development plan.
Use in children aged 6 to 11 years	
Risk minimisation measures	SmPC Sections 4.1, 4.2, and 4.4. PL Sections 1 and 2 Prescription only
Additional pharmacovigilance activities	• Open-label extension study (Study 107) See Section II.C of this summary for an overview of the post-authorisation development plan

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CF: cystic fibrosis; ELX/TEZ/IVA: elexacaftor in combination with tezacaftor and ivacaftor (also known as Trikafta); LFT: liver function test; PI: product information (product information for professionals); PL: Package Leaflet (product information for patients); Study 102: VX17-445-102; Study 107: VX19-445-107; ULN: upper limit of normal; UV: ultraviolet

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 Trikafta.

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

Post-authorisation safety study *(PASS)*
Purpose of the study: To evaluate the safety outcomes, CF disease progression, frequency and outcome of pregnancy, and drug utilisation patterns in CF patients taking ELX/TEZ/IVA in the real-world setting

Open-label extension study *(Study 107)*

Purpose of the study: To evaluate the long-term safety, tolerability, and efficacy and the pharmacodynamics of ELX/TEZ/IVA treatment for 96 weeks in subjects 6 years of age and older with CF, homozygous for *F508del-CFTR* mutation or heterozygous for *F508del-CFTR* and a minimal function mutation