VERTEX PHARMACEUTICALS INCORPORATED

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

Version 2 (20 January 2022)

Based on EU RMP Version 3.0 and Swiss-Specific Annex Version 2.0

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 the risks as well as to prevent or minimise them.

The RMP summary of Symdeko® 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 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 Symdeko® in Switzerland, is the "Arzneimittelinformation / Information sur le médicament" (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 Symdeko®.

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SUMMARY OF THE RISK MANAGEMENT PLAN FOR SYMDEKO (TEZACAFTOR/IVACAFTOR)

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

Symdeko's Product Information and its package information leaflet give essential information to healthcare professionals and patients on how Symdeko should be used.

Important new safety concerns or changes to the current safety concerns will be included in updates of the Symdeko RMP.

I. The medicine and what it is used for

Symdeko is authorised for the treatment of patients with cystic fibrosis (CF) aged 6 years and older who are homozygous for the *F508del* mutation or are heterozygous for the *F508del* mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G,* or *3849+10kbC→T*. Symdeko contains tezacaftor in combination with ivacaftor as the active substances in the morning dose and ivacaftor as the active substance in the evening dose. Symdeko is given orally.

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

Important risks of Symdeko, together with measures to minimise such risks and the proposed studies for learning more about Symdeko'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 Symdeko is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Symdeko 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 Symdeko. 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	• None
Important potential risks	• Hepatotoxicity • Concomitant use of TEZ/IVA with strong CYP3A inhibitors or inducers • Cataract
Missing information	• Use in pregnant and lactating women • Long-term safety • Patients with moderate or severe hepatic impairment • Patients with ppFEV$_1$ < 40

CYP: cytochrome P450; ppFEV$_1$: forced expiratory volume in 1 second; TEZ/IVA: tezacaftor in combination with ivacaftor

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Hepatotoxicity (important potential risk)	
Evidence for linking the risk to the medicine	Elevations in transaminases are common in patients with CF, and have been observed in some patients treated with TEZ/IVA, as well as with IVA monotherapy. Overall, the incidence of elevated liver function tests (LFTs) were well balanced between the TEZ/IVA or IVA monotherapy groups compared to the placebo group in the placebo controlled Phase 3 studies. However, in the IVA programme, increased ALT or AST has been reported slightly more frequently in the subset of patients with a medical history of elevated transaminases who received IVA monotherapy, compared to placebo. The potential role of IVA monotherapy or TEZ/IVA is uncertain, and cannot be fully excluded. The data from the open-label extension study in patients 12 years and older are consistent with the placebo-controlled trials.
Risk factors and risk groups	Only generally known risk factors for increases in LFTs were identified in several instances, including concurrent acute and chronic infections or illnesses (e.g., pulmonary exacerbation, flu like illness, haemoptysis, kidney infection), cystic fibrosis (CF), as well as concomitant drugs (e.g., acetaminophen, antibiotics) and substances (e.g., alcohol) known to be associated with LFT elevations.
Risk minimisation measures	**Routine risk minimisation measures:** PI "Warnings and precautions", "Undesirable effects" PI "Warnings and precautions" where advice is given on monitoring LFTs PL "When is caution required when taking Symdeko?", "How to use Symdeko" and "Possible side effects" Prescription only **Additional risk minimisation measures:** No risk minimisation measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Study 116 • Study 117 (PASS) See Section II.C of this summary for an overview of the post-authorisation development plan.

Concomitant use of TEZ/IVA with strong CYP3A inhibitors or inducers (important potential risk)	
Evidence for linking the risk to the medicine	The concurrent use of TEZ or IVA with other drugs that are CYP (cytochrome P450) 3A inhibitors and inducers can affect the exposure of TEZ and IVA. CYP3A inducers may reduce the therapeutic effectiveness of TEZ and IVA while CYP3A inhibitors can increase the exposures and, therefore, the incidence of ADRs. This risk is considered potential as it is based on nonclinical data and PK modelling, and has not been observed in humans so far, despite the known biologic plausibility.
Risk factors and risk groups	Patients treated with CYP3A strong inhibitors or inducers.
Risk minimisation measures	**Routine risk minimisation measures:** PI "Dosage/Administration", "Warnings and precautions", "Interactions" PI "Dosage/Administration", "Warnings and precautions", "Interactions" where dose reductions are recommended when TEZ/IVA is co-administered with a strong inhibitor of CYP3A. PL "When is caution required when taking Symdeko?" Prescription only **Additional risk minimisation measures:** No risk minimisation measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Study 116 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	Lens opacities (cataracts) were observed in newborn rats and were considered related to IVA treatment. This finding has not been observed in older animals. Given species developmental differences between rats and humans, it is unlikely that the finding is relevant to humans 12 years of age and older. There is a high background rate of cataract in patients with CF. The placebo controlled ocular safety data in the TEZ/IVA and IVA clinical development programmes did not suggest any imbalance in cataract incidence between the TEZ/IVA or IVA monotherapy groups compared to the placebo groups. Cases of non-congenital lens opacities were reported in paediatric subjects with TEZ/IVA or IVA monotherapy; these cases involved subtle ophthalmological findings with no impact on visual acuity, and a lack of progression. Although risk factors (e.g., corticosteroid use, exposure to radiation) were present in some cases, a contributing role of TEZ/IVA or IVA monotherapy cannot be completely excluded.
Risk factors and risk groups	Risk factors for cataracts include aging, trauma, ultraviolet light and radiation exposure, diabetes mellitus, intraocular inflammation, CF, and systemic or topical corticosteroid use.
Risk minimisation measures	**Routine risk minimisation measures:** PI "Warnings and Precautions", "Undesirable effects", and "Preclinical data" PI "Warnings and precautions" where advice is given on recommended ophthalmological examinations. PL "When is caution required when taking Symdeko?" and "Possible side effects" Prescription only **Additional risk minimisation measures:** No risk minimisation measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Study 116 See Section II.C of 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 to avoid the use of Symdeko during pregnancy and to determine the use during breastfeeding after taking into account the benefit of breastfeeding the child and the benefit of therapy for the woman. PL "Can Symdeko be taken during pregnancy and breastfeeding?" Prescription only
Additional pharmacovigilance activities	• Study 117 (PASS)
Long-term safety (missing information)	
Risk minimisation measures	PI "Undesirable effects" and "Properties/Effects" PI "Undesirable effects" and "Properties/Effects" describe the available clinical evidence, including the number and extent of exposure in clinical studies. Prescription only
Additional pharmacovigilance activities	• Study 116 • Study 117 (PASS)
Patients with moderate or severe hepatic impairment (missing information)	
Risk minimisation measures	PI "Dosage/Administration", "Warnings and precautions" and "Pharmacokinetics" PI "Dosage/Administration" where advice is given on dose adjustment based on severity of hepatic impairment. PL "When is caution required when taking Symdeko?" Prescription only
Additional pharmacovigilance activities	• Study 117 (PASS)
Patients with $ppFEV_1$ <40 (missing information)	
Risk minimisation measures	PI "Properties/Effects" Prescription only
Additional pharmacovigilance activities	• Study 117 (PASS)

ADR: adverse drug reaction; CF: cystic fibrosis; CYP: cytochrome P450; IVA: ivacaftor; LFT: liver function test; PK pharmacokinetics; PASS: Post-authorisation safety study; PI: product information (product information for professionals); PL: package leaflet (product information for patients); $ppFEV_1$: forced expiratory volume in 1 second; TEZ/IVA: tezacaftor in combination with ivacaftor

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 Symdeko.

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

Short study name: Study 117 (PASS)

Purpose of the study: Evaluate the utilisation patterns and real-world effects of TEZ/IVA therapy in patients with CF

Short study name: Study 116

Purpose of the study: Evaluate the safety and efficacy of long-term treatment with TEZ in combination with IVA in subjects aged 6 years and older with CF, homozygous or heterozygous for the *F508del-CFTR* mutation