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Swiss Summary of the Risk Management Plan for Orkambi® (lumacaftor/ivacaftor)

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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 Orkambi® 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 Orkambi® in Switzerland, is the "Arzneimittelinformation/ Information sur le medicament" (see www.swissmedic.ch), approved and authorised by Swissmedic.

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

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SUMMARY OF THE RISK MANAGEMENT PLAN (RMP) FOR ORKAMBI (LUMACAFTOR/IVACAFTOR)

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

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

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

I. The medicine and what it is used for

ORKAMBI tablets are authorised for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who are homozygous for the *F508del-CFTR* mutation. ORKAMBI granules are proposed for the indicated treatment of children with CF aged 2 to 5 years who are homozygous for the *F508del-CFTR* mutation.

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

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

II. A List of important risks and missing information

Important risks of ORKAMBI 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 ORKAMBI. 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.

List of important risks and missing information	
Important identified risks	• Respiratory events • Blood pressure increase • Hepatobiliary events
Important potential risks	• Cataracts • Cardiac arrhythmias
Missing information	• Use in pregnant and lactating women • Use in patients with organ transplant

II.B Summary of important risks

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

Respiratory events	
Evidence for linking the risk to the medicine	Some respiratory events (e.g., chest tightness and shortness of breath) were observed with Orkambi treatment. In two 24-week, placebo-controlled studies, most of these events were mild or moderate in severity and did not require discontinuation of Orkambi treatment. These events mostly occurred during the first week of treatment and resolved within a few days without a need to change the dose of Orkambi. Patients who were treated with Orkambi for up to 120 weeks did not show any worsening of these events over time. Respiratory events can be serious and can sometimes lead to stopping Orkambi treatment, particularly in patients with poor lung function. During a study in patients aged 6 through 11 years, a decrease in lung function test results was observed within hours of taking Orkambi. This decline in lung function mostly resolved after 2 weeks of treatment.
Risk factors and risk groups	General risk factors for respiratory events may include underlying CF and its associated pulmonary manifestations. Overall, respiratory events occur more frequently and tend to be more severe or lead to discontinuation in patients with lower $ppFEV_1$.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 and PL Section 2 where advice is given for additional monitoring in patients with $ppFEV_1$ <40. SmPC Section 4.8 PL Section 4 Prescription only **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Blood Pressure Increase	

Evidence for linking the risk to the medicine	Blood pressure increase was observed in some patients treated with Orkambi. During two 24-week, placebo-controlled studies, the percentage of subjects who had a systolic blood pressure value >140 mm Hg on at least 2 occasions was 3.4% in subjects in the total Orkambi group compared with 1.6% in subjects in the placebo group. The percentage of subjects who had a diastolic blood pressure value >90 mm Hg on at least 2 occasions was 1.5% in subjects in the total Orkambi group compared with 0.5% in subjects in the placebo group. Throughout the 24 weeks, 7 out of 738 patients treated with Orkambi had adverse events related to increased blood pressure compared to zero patients in the placebo group. All these adverse events were mild or moderate in severity; 1 was considered serious. When patients were treated with Orkambi for an additional 96 weeks (up to 120 cumulative weeks), the average blood pressure increased a small amount compared to the end of the placebo-controlled studies (Week 24). However, the average blood pressure still remained in the normal range and mostly occurred in patients who already had low blood pressure prior to starting Orkambi, including patients who were under 18 years of age and still growing. The blood pressure data in patients less than 12 years were consistent with those in patients aged 12 years and older.
Risk factors and risk groups	No risk factors have been identified.
Risk minimisation measures	**Routine risk minimisation measure:** SmPC Section 4.4 and PL Section 2 where advice is given for periodic monitoring of BP. SmPC Section 4.8 PL Section 4 Prescription only **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Hepatobiliary events	
Evidence for linking the risk to the medicine	Raised levels of liver enzymes called transaminases (ALT or AST) or liver-related side effects were reported in clinical studies with Orkambi. In two 24-week, placebo-controlled studies, these events occurred in similar proportions in patients who received Orkambi and placebo; however, more patients receiving Orkambi had serious liver-related side effects. Raised levels of ALT or AST associated with increases in total bilirubin concentrations occurred in 0.4% of patients treated with Orkambi. These elevations could be a sign of liver injury. Patients who were treated with Orkambi for up to 120 weeks did not show any worsening of these events. Seven patients who received Orkambi in clinical studies already had advanced liver disease. In 1 patient, liver function worsened after receiving Orkambi and only recovered after Orkambi was stopped. A study in patients with moderate liver impairment showed that blood levels of LUM and IVA increased in these patients. Studies have not been conducted in patients with severe liver impairment; however, it is expected that blood levels of LUM and IVA may increase more than in patients with moderate liver impairment. There have been reports of patients with pre-existing liver damage who had liver failure and died. Raised levels of ALT or AST were more common in younger patients (less than 12 years of age) with cystic fibrosis compared to older patients with cystic fibrosis. This finding was similar whether patients received Orkambi or placebo. Patients aged 2 years and older treated with Orkambi for up to 120 weeks did not show any worsening of these events.

Risk factors and risk groups	Hepatobiliary events are more common in patients with pre-existing liver disease or medical history of abnormal liver function tests. Patients with pre-existing cirrhosis and portal hypertension may have a greater risk of liver function decompensation, including a potential fatal outcome.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 and PL Section 2 where advice is given on monitoring LFTs. SmPC Sections 4.2, 4.4, and 5.2 and PL Section 3 where advice is given on dose adjustment based on severity of hepatic impairment. SmPC Section 4.8 PL Section 4 Prescription only **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Cataracts	
Evidence for linking the risk to the medicine	Lens opacities (cataracts) were observed in newborn rats and were considered IVA-related. This finding has not been observed in older animals. The potential relevance of these findings in humans is unknown, but given the developmental differences between rats and humans, it is unlikely that the finding is relevant to humans 2 years of age and older. In the IVA and Orkambi programmes, there have been some reports of non-congenital (not present since birth or the first year of life) lens abnormalities in patients. The majority of the reported events involved small findings and did not affect vision. The relationship of these events to IVA monotherapy and Orkambi therapy is uncertain because of the presence of other possible causes.
Risk factors and risk groups	Risk factors for cataracts include aging, trauma to the eye, ultraviolet light and radiation exposure, diabetes mellitus, intraocular (inside the eye) inflammation, and systemic or topical corticosteroid use.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 and PL Section 2 where advice is given on ophthalmological examinations in paediatric patients. SmPC Section 5.3 Prescription only **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Cardiac Arrhythmias	
Evidence for linking the risk to the medicine	This important potential risk of abnormal heartbeat is based on findings in dogs. In the clinical trials, abnormal heartbeat was reported in human patients who received Orkambi, but these events were few and also occurred in similar numbers of patients in the placebo group. Most of these events were not serious.
Risk factors and risk groups	No risk factors have been identified.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 5.3 Prescription only **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Use in pregnant and lactating women	
Risk minimisation measures	SmPC Section 4.6 and PL Section 2 where advice is given on the use of Orkambi during pregnancy and breastfeeding. SmPC Section 5.3 Prescription only
Additional pharmacovigilance activities	None
Use in patients with organ transplant	
Risk minimisation measures	SmPC Section 4.4 and PL Section 2 where advice is given that Orkambi use in this population is not recommended. SmPC Section 4.5 and PL Section 2 provide a list of immunosuppressants (used after organ transplant) with which concomitant use of Orkambi is not recommended. Prescription only
Additional pharmacovigilance activities	None

PL: patient leaflet; SmPC: Summary of Product Characteristics

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:

Study Name and Title: The Post-Authorisation Efficacy study (PAES) is an observational, registry-based study to evaluate the benefits of early initiation of LUM/IVA in CF patients aged 2 to 5 years who are homozygous for *F508del-CFTR*.

Rationale and Study Objectives:

The objective of this study is to evaluate benefits of early initiation of LUM/IVA

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

Not applicable