Summary of Risk Management Plan for ORKAMBI (lumacaftor/ivacaftor)

This is a summary of the 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 SmPC and its package leaflet (PL) give essential information to healthcare professionals and patients on how ORKAMBI should be used.

This summary of the RMP for ORKAMBI 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 ORKAMBI's RMP.

I. The medicine and what it is used for

ORKAMBI tablets are authorised for the treatment of CF in patients aged 6 years and older who are homozygous for the *F508del-CFTR* mutation. ORKAMBI granules are authorised for the indicated treatment of children with CF aged 1 to 5 years who are homozygous for the *F508del-CFTR* mutation. See SmPC for the full indication.

Further information about the evaluation of ORKAMBI's benefits can be found in ORKAMBI's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/orkambi.

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 PL 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 the case of ORKAMBI, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

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
Important potential risks	•Cataracts
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:** Study 124
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:** Study 124
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

CF: cystic fibrosis; IVA: ivacaftor; PL: package leaflet; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; 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*.

Note: The PAES will be expanded to evaluate patients who initiate LUM/IVA at 1 to less than 2 years of age.

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