PART VI Summary of the RMP

Summary of Risk Management Plan for KALYDECO (ivacaftor)

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

KALYDECO's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how KALYDECO should be used.

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

I. The medicine and what it is used for

KALYDECO tablets are authorised for the treatment of patients with cystic fibrosis (CF) in patients aged 6 years and older and weighing 25 kg or more who have an *R117H-CFTR* mutation or one of the following gating (class III) mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R*. KALYDECO tablets are also indicated in combination regimens:

- with tezacaftor/ivacaftor tablets for the treatment of patients with cystic fibrosis (CF) aged 6 years and older who are homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and have one of the following mutations in the *CFTR* gene: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T*; and
- with ivacaftor/tezacaftor/elexacaftor tablets for the treatment of patients with cystic fibrosis (CF) aged 6 years and older who have at least one *F508del* mutation in the *CFTR* gene.

KALYDECO granules are indicated for the treatment of children with cystic fibrosis (CF) aged 4 months and older and weighing 5 kg to less than 25 kg who have an *R117H-CFTR* mutation or one of the following gating (class III) mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R* (see SmPC for the full indication). KALYDECO granules are also indicated in combination regimens:

- with ivacaftor/tezacaftor/elexacaftor tablets for the treatment of patients with CF aged 2 years to less than 6 years who have at least one *F508del* mutation in the *CFTR* gene.

KALYDECO contains ivacaftor (IVA) as the active substance and is given orally.

Further information about the evaluation of KALYDECO's benefits can be found in KALYDECO'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/kalydeco.

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

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

II.A List of important risks and missing information

Important risks of KALYDECO 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 KALYDECO. 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	None
Important potential risks	• Hepatotoxicity • Cataract
Missing information	• Use in pregnant and lactating women • Indicated use in children aged less than 6 years

II.B Summary of important risks

Hepatotoxicity	
Evidence for linking the risk to the medicine	Elevated liver enzymes were reported during Phase 2b/3 studies with IVA; however, elevations in transaminases are common in patients with CF. The contributing role of IVA is uncertain but cannot be excluded.
Risk factors and risk groups	Only generally known risk factors for increases in liver enzymes were identified in several instances, including concurrent acute and chronic infections or illnesses (e.g., pulmonary exacerbation, flu-like illness, haemoptysis, kidney infection), as well as concomitant drugs (e.g., acetaminophen, antibiotics) and substances (e.g., alcohol) known to be associated with liver enzyme elevations.

Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 where advice is given on monitoring liver function tests. SmPC Section 4.8 PL Section 4 Prescription only **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study 126
Cataract	
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 species developmental differences between rats and humans, it is unlikely that the finding is relevant to humans 6 years of age and older. Non-congenital cataracts have been reported, although risk factors (e.g., corticosteroid use) were present, a contributing role of IVA 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, and systemic or topical corticosteroid use.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 where advice is given on recommended ophthalmological examinations SmPC Section 5.3 PL Section 2 Prescription only **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study 126
Use in pregnant and lactating women	
Risk minimisation measures	SmPC Section 4.6 where advice is given on to use Kalydeco during pregnancy only if clearly needed and during breastfeeding if the potential benefit outweighs the potential risks. PL Section 2 Prescription only
Additional pharmacovigilance activities	None
Indicated use in children aged less than 6 years	
Risk minimisation measures	SmPC Section 4.2 where the posology is described SmPC Sections 4.8 and 5.2 PL Section 2 Prescription only
Additional pharmacovigilance activities	Study 126

CF: cystic fibrosis; IVA: ivacaftor; PL: patient leaflet; SmPC: Summary of Product Characteristics
Note: Study 126 addresses a subpopulation of the Missing Information of "Indicated use in children aged less than 6 years."

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:

Short study name: Post-Authorisation Efficacy Study

Purpose of the study: The Post-Authorisation Efficacy Study (PAES) will evaluate whether long-term Kalydeco treatment slows disease progression in children. This study aims to confirm whether Kalydeco treatment in a "real-world" setting continues to positively impact

nutritional status and other measures of effectiveness, including, but not limited to, hospitalisations, pulmonary exacerbations, and pulmonary function, and to evaluate the long-term safety of Kalydeco treatment in this population. Because spirometry is challenging for children younger than 5 to 6 years of age and results may be unreliable, this long-term observational study will evaluate the effectiveness of Kalydeco in young patients with respect to lung function by following them for 6 years, allowing them to reach the age when lung function measurements are routinely performed and are more reliable.

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

Short study name: Study 126

Purpose of the study: Study 126 will evaluate the long-term safety, pharmacokinetics, pharmacodynamics, and efficacy of IVA in children aged <24 months when initiating IVA treatment. The 96-week IVA Treatment Period includes safety evaluations of adverse events, clinical laboratory assessments (serum chemistry and hematology), electrocardiograms, vital signs, physical examinations, and ophthalmological examinations.