Summary of risk management plan for Zykadia (ceritinib)

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

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

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

I. The medicine and what it is used for

Zykadia contains ceritinib as the active substance and it is used for the following indications:

- Zykadia as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib.
- Zykadia as monotherapy is indicated for the first line treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC)

The recommended dose of ceritinib is 450 mg once daily with food at the same time each day.

Further information about the evaluation of ceritinib's benefits can be found in ceritinib's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link to the EPAR summary landing page on the EMA webpage.

https://www.ema.europa.eu/en/documents/rmp-summary/zykadia-epar-risk-management-plan-summary_en.pdf

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of ceritinib, together with measures to minimize such risks and the proposed studies for learning more about ceritinib's risks, are outlined below.

Measures to minimize 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 minimize its risks.

Together, these measures constitute *routine risk minimization* 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 ceritinib's not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of ceritinib are risks that need special risk management activities to further investigate or minimize 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 ceritinib. 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);

Table-1 List of important risks and missing information

Important identified risks	None
Important potential risks	Risk for patients with severe hepatic impairment (including lack of efficacy)
Missing information	Pregnant and lactating women, and women of childbearing potential

II.B Summary of important risks

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

Table-2 Important potential risk: Risk for patients with severe hepatic impairment (including lack of efficacy)

Evidence for linking the risk to the medicine	Preclinical studies indicated that ceritinib clearance pathways are likely to have some hepatic involvement. Biliary excretion is expected to have the largest role in the hepatic component of drug elimination, with a potential more minor role of hepatic metabolic enzymes. Therefore, alterations of hepatobiliary excretory and metabolic activities might lead to higher exposures and greater drug accumulation of ceritinib in the hepatically impaired population. The effect of ceritinib in patients with various degrees of hepatic impairment was studied in the Study A2110, which demonstrated similar effects. The mean systemic exposure ($AUC_{inf)}$ to ceritinib was increased in subjects with severe hepatic impairment as compared to healthy subjects; physiology-based PK modeling, however, predicted the exposure to ceritinib to be similar between patients and healthy subjects under steady-state conditions. No relevant increase in exposure was seen in patients with moderate hepatic impairment.
Risk factors and risk groups	Patients with severe hepatic impairment patients who receive ceritinib.
Risk minimization measures	**Routine risk minimization measures** SmPC Sections 4.2, 4.4 and 4.5 **Additional risk minimization measures** None

Table-3 Missing information: Pregnant and lactating women, and women of childbearing potential

Risk minimization measures	**Routine risk minimization measures** SmPC Section 4.6 and Section 5.3 **Additional risk minimization measures** None

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 authorization or specific obligation of ceritinib.

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

Table-4 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
LDK378A2303, A Phase III, multicenter, randomized, open-label study of oral LDK378 versus standard chemotherapy in adult patients with ALK rearranged (ALK-positive) advanced non-small cell lung cancer who have been treated previously with chemotherapy (platinum doublet) and crizotinib. **Status**: Ongoing.	The primary objective is to compare the antitumor activity of ceritinib versus reference chemotherapy, as measured by PFS determined by a (BIRC).