**Summary of risk management plan for XALKORI**

This is a summary of the RMP for XALKORI. The RMP details important risks of XALKORI, how these risks can be minimised, and how more information will be obtained about XALKORI's risks.

XALKORI's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how XALKORI should be used.

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

**I. The Medicine and What It Is Used For**

XALKORI is authorised for

- the first-line treatment of adults with ALK-positive advanced NSCLC, for the treatment of adults with previously treated ALK-positive advanced NSCLC and for the treatment of adults with ROS1-positive advanced NSCLC. It contains crizotinib as the active substance and it is given by oral route of administration.
- (proposed) treatment of paediatric patients (age ≥6 to <18 years) with relapsed or refractory systemic anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL).
- (proposed) treatment of paediatric patients (age ≥6 to <18 years) with recurrent or refractory anaplastic lymphoma kinase (ALK)-positive unresectable inflammatory myofibroblastic tumour (IMT).

Further information about the evaluation of XALKORI's benefits can be found in XALKORI'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:
https://www.ema.europa.eu/en/medicines/human/EPAR/xalkori

**II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks**

Important risks of XALKORI, together with measures to minimise such risks and the proposed studies for learning more about XALKORI'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 the case of crizotinib, these measures are supplemented with *additional risk minimisation* measures mentioned under relevant important risks, see below.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

## II.A List of Important Risks and Missing Information

Important risks of XALKORI 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 XALKORI. 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 | • Hepatotoxicity<br>• Pneumonitis/ILD<br>• QTc Prolongation<br>• Bradycardia<br>• Renal Cyst<br>• Gastrointestinal perforation[a]<br>• Cardiac failure[b] |
| Important potential risks | • Reproductive Toxicity (including pregnant and lactating women)<br>• Severe Vision Loss/Potential Sight Threatening Event<br>• Bone Toxicity and Impaired Bone Growth in the Paediatric Population |
| Missing information | • Patients undergoing long-term treatment |

ILD = Interstitisal Lung Disease.

a. Considered as an important identified risk in the EU and Switzerland.

b. Considered as an important identified risk in the EU, Japan, Switzerland and other ex-US countries.

## II.B Summary of Important Risks

### Table 2. Summary of Important Risks

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|---|---|
| **Important Identified Risk: Hepatotoxicity** | |
| Evidence for linking the risk to the medicine: | All non-clinical and all company-sponsored clinical studies; and post-marketing reports. |
| Risk factors and risk groups: | There are currently no known risk groups or risk factors for the development of hepatotoxity in patients receiving crizotinib. |
| Risk minimisation measures: | Routine risk minimisation measures:<br>SmPC sections 4.2, 4.4, 4.8<br><br>Additional risk minimisation measures:<br>Educational Materials |
| **Important Identified Risk: Pneumonitis/Interstitial Lung Disease** | |
| Evidence for linking the risk to the medicine: | All non-clinical and all company-sponsored clinical studies; and post-marketing reports. |
| Risk factors and risk groups: | There are currently no known risk groups or risk factors for the development of pneumonitis/ILD in patients receiving crizotinib. Factors that could potentially be associated with an increased risk of developing pneumonitis/interstitial lung disease under ongoing treatment with crizotinib include a history of pre-existing pulmonary disease, prior or concomitant treatment with medications with known pulmonary toxicity: antibiotics (nitrofurantoin, amphotericin B, minocycline); chemotherapy (bleomycin, methotrexate, cyclophosphamide); antiarrhythmics (amiodarone), radiation therapy, immune suppression resulting in pneumonia (bacterial, viral, fungal, or protozoal), a predisoposition to allergic pulmonary disease, autoimmune diseases (SLE, rheumatoid arthritis, etc.), occupational exposure (smoke, dust, silicone, asbestos), and other factors. Further, the underlying malignancy, particularly lymphangiosis carcinomatosa may also increase the risk of pneumonitis and additionally confound the diagnosis. |
| Risk minimisation measures: | Routine risk minimisation measures:<br>SmPC sections 4.2, 4.4, 4.8<br><br>Additional risk minimisation measures:<br>Educational Materials |
| **Important Identified Risk: QTc Prolongation** | |
| Evidence for linking the risk to the medicine: | All non-clinical and all company-sponsored clinical studies; and post-marketing reports |
| Risk factors and risk groups: | No specific risk factors have been identified which may predispose patients to develop symptomatic QTc prolongation as a result of treatment with crizotinib.<br><br>Based on known general risk factors for QTc prolongation, patient factors that may potentially be associated with an increased risk of developing QTc prolongation under treatment with crizotinib may include pre-existing conditions such as a Long QT Syndrome, a history of cardiac dysrhythmia, electrolyte disturbances, cardiac ischemia, and the concomitant use of medications with the potential to prolong QTc. |
| Risk minimisation measures: | Routine risk minimisation measures:<br>SmPC sections 4.2, 4.4, 4.8, 5.2<br><br>Additional risk minimisation measures:<br>Educational Materials |

## Table 2. Summary of Important Risks

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| **Important Identified Risk: Bradycardia** | |
| Evidence for linking the risk to the medicine: | All non-clinical and all company-sponsored clinical studies; and post-marketing reports. |
| Risk factors and risk groups: | No specific risk groups or risk factors have been identified that might predispose patients to the development of bradycardia. However, pre-existing bradycardia, sinus node dysfunction, atrioventricular conduction disturbances, as well as concomitant medications affecting heart rate, such as beta blockers and non-dihydropyridine calcium channel blockers may increase the risk of developing bradycardia. |
| Risk minimisation measures: | Routine risk minimisation measures:<br>SmPC sections 4.2, 4.4, 4.5, 4.8<br><br>Additional risk minimisation measures:<br>Educational Materials |
| **Important Identified Risk: Renal Cyst** | |
| Evidence for linking the risk to the medicine: | All non-clinical and all company-sponsored clinical studies; and post-marketing reports. |
| Risk factors and risk groups: | It is possible that patients with pre-existing renal cysts are at increased risk of developing new (or enlarged) renal cysts under crizotinib. |
| Risk minimisation measures: | Routine risk minimisation measures:<br>SmPC sections 4.8<br><br>Additional risk minimisation measures:<br>Educational Materials |
| **Important Identified Risk: Gastrointestinal Perforation** | |
| Evidence for linking the risk to the medicine: | All non-clinical and all company-sponsored clinical studies; and post-marketing reports. |
| Risk factors and risk groups: | Patients with conditions such as history of diverticulitis, metastases to the gastrointestinal tract, or concomitant use of medications with a recognized risk of gastrointestinal perforation are predisposed to developing gastrointestinal perforation. |
| Risk minimisation measures: | Routine risk minimisation measures:<br>SmPC sections 4.4, 4.8<br><br>Additional risk minimisation measures:<br>Educational Materials |
| **Important Identified Risk: Cardiac failure** | |
| Evidence for linking the risk to the medicine: | All non-clinical and all company-sponsored clinical studies; and post-marketing reports. |
| Risk factors and risk groups: | No clear risk factors have been identified. It is theoretically possible that patients with a history of cardiac disease, cardiac risk factors, or prior therapy with cardiotoxic drugs have a higher risk developing ventricular dysfunction while receiving crizotinib. |
| Risk minimisation measures: | Routine risk minimisation measures:<br>SmPC sections 4.4<br><br>Additional risk minimisation measures:<br>Educational Materials |

**Table 2. Summary of Important Risks**

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|---|---|
| **Important Potential Risk: Reproductive Toxicity (including pregnant and lactating women)** | |
| Evidence for linking the risk to the medicine: | All non-clinical and all company-sponsored clinical studies; and post-marketing reports. |
| Risk factors and risk groups: | Risk factors and risk groups include women of childbearing potential, pregnant women, and lactating women. |
| Risk minimisation measures: | Routine risk minimisation measures:<br>SmPC sections 4.6, 5.3<br><br>Additional risk minimisation measures:<br>Educational Materials |
| **Important Potential Risk: Severe Vision Loss/Potential Sight Threatening Event** | |
| Evidence for linking the risk to the medicine: | All non-clinical and all company-sponsored clinical studies; and post-marketing reports. |
| Risk factors and risk groups: | Risk groups or risk factors associated with increased risk of severe vision loss/potential sight threatening event after administration of crizotinib is unknown. Cases of severe vision loss have been associated with brain metastases. |
| Risk minimisation measures: | Routine risk minimisation measures:<br>SmPC sections 4.2, 4.4, 4.7, 4.8<br><br>Additional risk minimisation measures:<br>Educational Materials<br>DHCP (specific to the paediatric population) |
| **Important Potential Risk: Bone Toxicity and Impaired Bone Growth in the Paediatric Population** | |
| Evidence for linking the risk to the medicine: | Non-clinical and non-MAH sponsored clinical studies |
| Risk factors and risk groups: | Risk factors and risk groups include paediatric patients. |
| Risk minimisation measures: | Routine risk minimisation measures:<br>SmPC section 5.3<br><br>Additional risk minimisation measures:<br>None |

## 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:

None

### II.C.2 Other Studies in Post-Authorisation Development Plan

**Study name:** CRISP Study ITCC 053: A phase 1B of crizotinib either in combination or as single agent in pediatric patients with ALK, ROS1 or MET positive malignancies.

**Purpose of the study:** To evaluate the risk factors manifestations, and outcomes of ocular toxicities associated with crizotinib in paediatric and young adult patients

Study name: CRZ-NBALCL Study (Protocol WI218627): A phase I/II study of crizotinib for recurrent or refractory ALK-positive ALCL and phase I study of this drug for recurrent or refractory neuroblastoma (Japan).

Purpose of study: To evaluate the AEs of bone toxicity and impaired bone growth and ocular toxicity with crizotinib as a single agent in paediatric and young adult patients.