PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

XALKORI® (Crizotinib)

Marketing Authorization Number 62131

Hard capsules, 200 mg, 250 mg

Document Version: 1.0

Document Date: 05 May 2022

Based on Part VI of EU RMP version 8.0, dated 06 May 2021

Pfizer AG, Schärenmoosstrasse 99, CH-8052 Zürich

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OVERVIEW

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 for Xalkori is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g., by mentioning risks occurring in populations or indications not included in the Swiss marketing authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Xalkori in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic. Pfizer is fully responsible for the accuracy and correctness of the content of the published RMP summary of Xalkori.

SUMMARY OF RISK MANAGEMENT PLAN FOR XALKORI (CRIZOTINIB)

This is a summary of the Risk Management Plan (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 and uncertainties (missing information).

XALKORI's proposed Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to Healthcare Professionals (HCPs) 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 unresectable, recurrent, or refractory anaplastic lymphoma kinase (ALK)-positive 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.

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 • Pneumonitis/ILD • QTc Prolongation • Bradycardia • Renal Cyst • Gastrointestinal perforation[a] • Cardiac failure[b]
Important Potential Risks	• Reproductive Toxicity (including pregnant and lactating women) • Severe Vision Loss/Potential Sight Threatening Event
Missing Information	• Patients undergoing long-term treatment

ILD = Interstitial 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

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.

Table 2. Summary of Important Risks

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: SmPC sections 4.2, 4.4, 4.8 Additional risk minimisation measures: 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 predisposition 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: SmPC sections 4.2, 4.4, 4.8 Additional risk minimisation measures: 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. 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: SmPC sections 4.2, 4.4, 4.8, 5.2 Additional risk minimisation measures: Educational Materials
Important Identified Risk: Bradycardia	

Table 2. Summary of Important Risks

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: SmPC sections 4.2, 4.4, 4.5, 4.8 Additional risk minimisation measures: 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: SmPC sections 4.8 Additional risk minimisation measures: 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: SmPC sections 4.4, 4.8 Additional risk minimisation measures: 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: SmPC sections 4.4

Table 2. Summary of Important Risks

	Additional risk minimisation measures: Educational Materials
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: SmPC sections 4.6, 5.3 Additional risk minimisation measures: 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: SmPC sections 4.2, 4.4, 4.7, 4.8 Additional risk minimisation measures: Educational Materials

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 short name: Study A8081062 - A Descriptive Study of Severe Visual Loss Following Exposure to XALKORI (crizotinib)

Purpose of the study: This is a post-authorisation safety study required by the US FDA to evaluate the frequency of risk factors for and sequelae of severe visual loss among patients being treated with crizotinib.