ALECENSA®
150 mg, Hartkapseln
Zul.-Nr. 65‘970

Public Risk Management Plan (RMP) Summary

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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 minimize them. The RMP summary of Alecensa® 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“ approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Alecensa® in Switzerland is the „Arzneimittelinformation“ (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Roche Pharma (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the here published RMP summary of Alecensa®.

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR ALECTINIB (ALECENSA)

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

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

This summary of the RMP for Alecensa 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 Alecensa RMP..

I. THE MEDICINE AND WHAT IT IS USED FOR

Alecensa is authorized for the treatment (as monotherapy) of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib. Additionally, alecensa 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). It contains alectinib as the active substance and it is given by oral administration.

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

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Alecensa, together with measures to minimize such risks and the proposed studies for learning more about Alecensa 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 authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

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- 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 minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, 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 Alecensa is not yet available, it is listed under 'Missing Information' below.

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of Alecensa 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 Alecensa. 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).

List of important risks and missing information	
Important identified risks	• Interstitial lung disease/pneumonitis • Hepatotoxicity • Photosensitivity • Bradycardia • Severe myalgia and CPK elevations
Important potential risks	• Embryo-fetal toxicity
Missing information	• Long-term safety

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II.B SUMMARY OF IMPORTANT RISKS

Important identified risks: Interstitial Lung Disease (ILD)/Pneumonitis	
Evidence for linking the risk to the medicine	ILD may be a problematic diagnosis and this is particularly evident in patients with advanced or metastatic cancer. The respiratory symptoms of ILD cannot be distinguished from progressive tumor or lower respiratory tract infections, and these symptoms may constitute the main differential diagnosis in this patient population. This is further compounded by the difficulty in obtaining histological samples to confirm ILD, and computed tomography scans may not point to a diagnosis (Danson et al. 2005). Furthermore, lung radiotherapy can cause symptomatic radiation pneumonitis within 1-6 months after the completion of radiotherapy. The incidence of any grade radiation pneumonitis was 49% in a single-center study of locally advanced or medically inoperable lung cancer patients, with most pneumonitis cases being classified as "mild" (Inoue et al. 2001). Mild and severe radiation pneumonitis occurred in 69 (36%) and 25 (13%) patients, respectively, in a singlecenter study of locally advanced or medically inoperable lung cancer patients (191 evaluable patients) who had undergone irradiation of the chest. Only severe radiation pneumonitis was an adverse prognostic factor. Low PaO2 (<80 torr) before radiotherapy was a significant risk factor predictive of severe radiation pneumonitis. The role of corticosteroids in radiation pneumonitis could not be accurately determined. The study was conducted in Japan where there are high rates of ILD reporting. Similarly, Parashar et al. (2011) reported that 52% of patients developed grade ≥2 radiation pneumonitis in association with chemotherapy. According to the authors, the reported rate of developing radiation pneumonitis in patients receiving definitive radiation therapy for lung cancer "is 5%

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	to 36% however, this incidence is probably underreported because of the nonspecific symptoms of radiation pneumonitis that may be erroneously attributed to another cardiovascular or respiratory disorder." Two other studies reported an incidence of 13% (Schallenkamp et al. 2007) and 16% (Kwa et al. 1998). In previous epidemiologic studies in multiple tumor types, it has been estimated that less than 10% of patients who receive chemotherapy develop pulmonary toxicities (Limper 2004), which include ILD. Estimates from epidemiologic studies on the rate of ILD in NSCLC range from around 1%-4%, though specific definitions may vary between studies (Voltolini et al. 2013). Two large Japanese studies estimated that approximately 2.1%-2.4% of NSCLC patients had or developed ILD, with adverse impact on survival (Kudoh et al. 2008; Miyazaki et al. 2009). Many of the first- and second-line NSCLC chemotherapeutic agents, such as gemcitabine and carboplatin are associated with lung toxicities. Gemcitabine-induced pulmonary toxicity is well documented with an incidence of 0%-5%, and mortality rate of 20% in those who develop this complication (Barlesi et al. 2004). Among patients treated with gemcitabine, the incidence of pulmonary fibrosis (Grade unspecified) was 28.1% in a large, observational US based cohort of 72,165 NSCLC patients (all stages were included) based on SEER-Medicare data (Hardy et al. 2010). One case of alectinib-induced severe interstitial lung disease has been reported in the literature (Yamamoto et al. 2015).
Risk factors and risk groups	ILD is considered a class effect of ALK inhibitors. Currently, there are no known risk groups or risk factors for ILD in patients treated with alectinib, and its development remains unpredictable and idiosyncratic.

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	In general, factors that could potentially be associated with an increased risk of drug-induced ILD include: history of pre-existing lung disease, radiation, prior or concomitant treatment with medications with known pulmonary toxicity (e.g., some antimicrobial, anti-inflammatory and cardiovascular agents, biologics, chemotherapeutics), inflammatory conditions (e.g., rheumatoid arthritis, inflammatory bowel disease), increased age, oxidative stress in the lung tissue due to reactive oxygen species, potentially ethnicity, and other (Schwaiblmair et al. 2012). Finally, the underlying malignant disease itself may increase the risk of pneumonitis and be a confounder of diagnosis.
Risk minimisation measures	Routine risk minimisation measures: *Routine risk communication:* SmPC Section 4.2 Posology and Method of Administration, Special Populations SmPC Section 4.4 Special Warnings and Precautions for Use SmPC Section 4.8 Undesirable Effects, Description of Selected Adverse Reactions Medicinal product subject to restricted medical prescription. *Additional risk minimisation measures:* None

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Additional pharmacovigilance activities	Alectinib survey to prescribers
Important identified risks: Hepatotoxicity	
Evidence for linking the risk to the medicine	In a review of 37 trials among NSCLC patients treated with cisplatin or carboplatin regimens, the frequency of reported liver abnormalities ranged from 1%-5%. The frequency of more severe liver injury was <1%. A comorbidity analysis of an international phase III trial in advanced NSCLC, which included 402 patients, reported liver disease in 9% of patients at baseline (Grønberg et al. 2010). Liver function test abnormalities can occur in patients with liver metastases. In an internal analysis, among a cohort of 121 patients with metastatic NSCLC and exposure to ALK inhibitors (from two Thomson Reuters MarketScan Research Databases 2009 – 2013) the incidence of liver injury was 4.0 per 100 ersonyears. No patients had a history of liver injury at diagnosis for metastatic NSCLC [internal data analysis; data available upon request].
Risk factors and risk groups	Pre-existing liver disease, including liver metastases, and hepatotoxic co-medications are risk factors for hepatotoxicity.
Risk minimisation measures	Routine risk minimisation measures: *Routine risk communication:* SmPC Section 4.2 Posology and Method of Administration, Special Populations SmPC Section 4.4 Special Warnings and Precautions for Use SmPC Section 4.8 Undesirable Effects, Description of

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	Selected Adverse Reactions Medicinal product subject to restricted medical prescription. *Additional risk minimisation measures:* None

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Additional pharmacovigilance activities	Alectinib survey to prescribers
Important identified risks: Photosensitivity	
Evidence for linking the risk to the medicine	No published literature is available to describe the background incidence/prevalence of photosensitivity in the lung cancer population. In an internal analysis, among a cohort of almost 20,000 lung cancer patients with a code for metastatic disease (from the United States [US] MarketScan claims database 2009 – 2013) the prevalence of photosensitivity diagnoses was 1% [internal data analysis; data available upon request].
Risk factors and risk groups	Specific risk factors or risks groups have not been identified.
Risk minimisation measures	Routine risk minimisation measures: *Routine risk communication:* SmPC Section 4.4 Special Warnings and Precautions for Use Medicinal product subject to restricted medical prescription. *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	Alectinib survey to prescribers
Important identified risks: Bradycardia	
Evidence for linking the	Bradycardia is often asymptomatic and therefore rarely reported in NSCLC, and there is a paucity of population-

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risk to the medicine	based literature on the frequency. Among 131 lung cancer patients (mean age 68 ± 9 years) at a Japanese hospital who underwent lung cancer resection between January 2005 and December 2006, 16 cases of arrhythmia, including one case of sinus bradycardia, were reported as a complication of lung cancer resection (Isobe et al. 2008). In an internal analysis, among a cohort of almost 20,000 lung cancer patients with a code for metastatic disease (from the United States [US] MarketScan claims database 2009 – 2013) the prevalence of reported bradycardia diagnoses was 3.4%, and QT prolongation 5.6%. In those patients with exposure to ALK inhibitors, the reported prevalence of bradycardia and QT prolongation was 5% and 3.3%, respectively [internal data analysis; data available upon request]. Under-reporting may impact the prevalence estimates of asymptomatic changes. However, a dose response relationship has been reported between bradycardia and crizotinib in NSCLC patients (Girard et al. 2014). A retrospective chart review of 42 patients with stage IV ALK-positive NSCLC from the PROFILE 1001 or 1005 crizotinib randomized controlled trials reported that 90.4% of the patients (n=38) experienced at least 1 episode of an absolute decrease in heart rate of more than 10 beats per minute (bpm) and 69% (n=29) of the patients experienced one episode of sinus bradycardia, defined as heart rate <60 bpm (Ou et al. 2013).
Risk factors and risk groups	Bradycardia is considered a class effect of ALK inhibitors. Known risk factors for bradycardia are age, pre-existing bradycardia, concurrent cardiovascular disease, and concomitant use of negative chronotrophic medications (e.g., beta-receptor blockers, non-dihydropyridine calcium channel blockers, antiarrhythmics, clonidine and digoxin).
Risk minimisation	Routine risk minimisation measures:

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measures	*Routine risk communication:* SmPC Section 4.2 Posology and Method of Administration, Special Populations SmPC Section 4.4 Special Warnings and Precautions for Use SmPC Section 4.8 Undesirable Effects, Description of Selected Adverse Reactions Medicinal product subject to restricted medical prescription. *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	Alectinib survey to prescribers
Important identified risks: Severe myalgia and CPK elevations	
Evidence for linking the risk to the medicine	In an internal analysis, among a cohort of 182 patients with metastatic NSCLC and exposure to ALK inhibitors (from two Thomson Reuters MarketScan® Research Databases 2009 – 2013) the prevalence of myositis and myalgia was 4.4% and the prevalence of CPK increase was 1.1%. The incidence of myositis and myalgia was 3.853 patients per 100 personyears while the incidence of CPK increase was 3.886 patients per 100 person-years [internal data analysis; data available upon request].

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Risk factors and risk groups	There are currently no known risk factors for alectinib. For the statin-induced myopathy, the following risk factors have been described: age, female gender, low BMI, polypharmacy, renal insufficiency, diabetes, rigorous exercise, alcohol consumption (Smithson 2009). For alectinib a numerical imbalance by gender has been observed in the pivotal Phase II trials, with women displaying more muscular AEs or CPK elevations requiring dose modification.
Risk minimisation measures	Routine risk minimisation measures: *Routine risk communication:* SmPC Section 4.2 Posology and Method of Administration, Special Populations SmPC Section 4.4 Special Warnings and Precautions for Use SmPC Section 4.8 Undesirable Effects, Description of Selected Adverse Reactions Medicinal product subject to restricted medical prescription. *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	Alectinib survey to prescribers
Important potential risk: Embryo-fetal toxicity	
Evidence for linking the risk to the medicine	The evidence comes from nonclinical studies. The underlying mechanisms of the observed embryo-lethality and fetal malformations in animals have not been elucidated. A maternal dose of alectinib equivalent to approximately 3-times the recommended human dose of 600 mg twice-daily

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	caused embryo-fetal loss (miscarriage) in pregnant rabbits. The same equivalent dose given to pregnant rats resulted in small fetuses with retarded ossification and minor abnormalities of the organs.

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Risk factors and risk groups	Female patients of child-bearing potential, women of childbearing potential who are partners of male patients receiving Alecensa, and neonates who are exposed to Alecensa during gestation
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special Warnings and Precautions for Use *Routine risk communication:* SmPC Section 4.6 Fertility, Pregnancy, and Lactation Medicinal product subject to restricted medical prescription. *Additional risk minimisation measures:* No additional risk minimisation measures
Additional pharmacovigilance activities	None
Missing information: Long-term safety	
Evidence for linking the risk to the medicine	Currently, there is no indicator to suggest a different safety profile in patients exposed longer to alectinib from clinical studies or post-marketing experience.
Risk factors and risk groups	Patients exposed to alectinib in the approved indication.
Risk minimisation measures	*Routine risk minimisation measures:* Continued clinical trial monitoring. *Routine risk communication:*

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	None Medicinal product subject to restricted medical prescription. *Additional risk minimisation measures:* No additional risk minimisation measures
Additional pharmacovigilance activities	None

AE = adverse event; CPK = creatinine phosphokinase; ILD = interstitial lung disease; SmPC = Summary of Product Characteristics.

II.C POST-AUTHORISATION DEVELOPMENT PLAN

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization.

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

Study short name: Alectinib survey to prescribers

Purpose of the study:

Primary Objective: To evaluate the effectiveness of Alecensa's risk minimisation activities of the important identified risks as per the label by investigating its correct implementation among HCPs.

Specific Objectives:

1) What is the HCPs' awareness of Alecensa's specific clinical measures to address important identified risks of ILD/pneumonitis, hepatotoxicity, bradycardia, phototoxicity, severe myalgia and CPK elevations in the SmPC.

2) What is the HCPs' knowledge on requirement for specific dose modifications for the following important identified risks: Interstitial Lung Disease (ILD)/Pneumonitis, hepatotoxicity, bradycardia, and severe myalgia and CPK elevations.

3) What is the HCPs' knowledge on requirement for specific monitoring or measures for the following important identified risks: Interstitial Lung Disease (ILD)/Pneumonitis, hepatotoxicity, severe myalgia and

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CPK elevations.

4) Other research questions are: Do HCPs' follow the SmPC recommendations? To what extent do HCPs consider the SmPC recommendations to be useful?

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