NOVARTIS

Patient Safety & Pharmacovigilance

Ceritinib

LDK378

EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Ceritinib
Product(s) concerned (brand name(s)):	Zykadia®
Document status:	Final
Version number:	18.0
Data lock point for this RMP	DLP for PAES study (LDK378A2303) 02-May-2024
Date of final sign off	31-May-2024

Rationale for submitting an updated RMP: The Risk Management Plan, EU RMP version 18.0, has been updated to capture the completion of RMP commitment of PAES Study (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.

Summary of significant changes in this RMP: When compared to the RMP version 17.0, the following changes have been made to the current RMP (version 18.0).

Part	Major changes compared to RMP v 17.0
Part I	No changes.
Part II	**Module SI:** No changes. **Module SII:** No changes. **Module SIII:** No change. **Module SIV:** Updated LDK378X2103 study status as completed. **Module SV:** No change. **Module SVI**: No change. **Module SVII**: Updated no changes in the risks in the new safety concerns and reclassification with a submission section. **Module SVIII:** No change.
Part III	No change.
Part IV	Removal of LDK378A2303 efficacy data.
Part V	No change.
Part VI	Removal of LDK378A2303 from post-authorization development plan.

Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within procedure number
CCI	CCI	CCI

Details of the currently approved RMP:

Version number: RMP version 17.0

Approved with procedure: EMEA/H/C/003819/R/0042

Date of approval (opinion date): 16-Feb-2022

Name of the QPPV: Dr Justin Daniels

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorization's holder QPPV. The electronic signature is available on file.

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse Event
ALK	Anaplastic Lymphoma Kinase
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BIRC	Blinded Independent Review Committee
bpm	beats per minute
CDS	Core data sheet
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CNS	Central nervous system
CRF	Case Report Form
CLcr	Creatinine Clearance
CSR	Clinical Study Report
DDI	Drug-Drug Interaction
DILI	Drug-induced liver injury
ECG	Electrocardiogram
EEA	European Economic Area
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
hERG	Human ether-a-go-go-related gene
HR	Heart rate
ILD	Interstitial lung disease
INR	International normalized ratio
INSR	Insulin receptor
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
PFS	Progression-free survival
PAES	Post-authorization efficacy study
P-gp	P-glycoprotein
PK	Pharmacokinetics
PPI	Proton pump inhibitor

PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred Term
RMP	Risk Management Plan
SAE	Serious adverse event
SCP	Single cell protein
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
TBILI	Total Bilirubin
TSH	Thyroid stimulating hormone
ULN	Upper Limit of Normal

1 Part I: Product(s) Overview

Table 1-1 Part I - Product Overview

Active substance(s) (INN or common name)	Ceritinib
Pharmacotherapeutic group(s) (ATC Code)	Anaplastic lymphoma kinase (ALK) inhibitor (ATC code: L01ED02)
Marketing Authorization Holder	Novartis Europharm Limited
Medicinal products to which this RMP refers	Zykadia/ceritinib
Invented name(s) in the European Economic Area (EEA)	Zykadia®
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Antineoplastic agent - anaplastic lymphoma kinase (ALK) inhibitor.
	Summary of mode of action: Ceritinib is a highly selective and potent ALK inhibitor which inhibits auto phosphorylation of ALK, ALK-mediated phosphorylation of downstream signaling proteins, and proliferation of ALK-dependent cancer cells.
	Important information about its composition: Ceritinib is of chemical origin. 5-Chloro-N2-[2-isopropoxy-5-methyle-4(4-piperidinyl)phenyl]-N4-[N4-[2-isopropylsulfonyl)phenyl]-2,4-pyrimidinediamine
Hyperlink to the Product Information	[Current approved SmPC]
Indication(s) in the EEA	**Current:** 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)
	Proposed: Not applicable
Dosage in the EEA	**Current:** Oral use. The recommended dose of ceritinib is 450 mg once daily with food at the same time each day.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** Film coated tablet, 150 mg and Hard gelatin capsule, 150 mg.

Is/will the product be subject to additional monitoring in the EU?	No

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1 Indication

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).

Zykadia as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib.

Incidence:

Lung cancer has been the most common cancer in the world for several decades, and in 2012, there were an estimated 1.8 million new cases worldwide, representing 12.9% of all new cancers, according to the GLOBOCAN project of the World Health Organization and the International Agency for Research on Cancer (GLOBOCAN 2012). The majority of the cases now occur in the less developed regions (58%). The estimated number of patients diagnosed with lung cancer in 2012 was 409911 in Europe and 309589 in the 27 member states of EU (EUCAN 2012a, EUCAN 2012b, EUCAN 2012c, Ferlay et al 2013). It is estimated that there were 222,500 new cases of lung cancer in the US in 2017 (SEER 2017).

NSCLC accounts for the majority of cases (~85%) of lung cancer. Using data on incident lung cancer cases in a regional cancer registry in Italy from 2000 through 2003, Pagano et al (2010) reported 2572 cases of NSCLC which represented 90% of all incident lung cancers. A Spanish study of 481 lung cancers diagnosed in a defined health area from February 1997 through December 1999 reported that approximately 80% were NSCLC (Prim et al 2010).

Improved knowledge of NSCLC biology has led to the identification of molecular events crucial for malignant transformation and cancer cell survival and “molecular subsets” of NSCLC patients who may be candidates for targeted therapy. Anaplastic lymphoma kinase, a receptor tyrosine kinase, was first identified as a fusion protein resulting from chromosomal translocation in the majority of anaplastic large cell lymphomas. When fused to other proteins, ALK becomes constitutively active, leading to increased catalytic kinase function, signal transduction activity, and oncogenic function. ALK has since been linked with many different fusion partners in different tumor types (Soda et al 2007, Shaw et al 2013). ALK gene rearrangements or the resulting fusion proteins may be detected in tumor specimens using fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), and reverse transcription polymerase chain reaction of cDNA (RT-PCR) (Shaw and Solomon 2014). The frequency of ALK gene rearrangements in patients with NSCLC (ALK positive NSCLC) is present in approximately 2% to 8% of tumors tested (Soda et al 2007, Takeuchi et al 2009, Kwak et al 2010, Scagliotti et al 2012).

Table 2-1 Incidence of lung cancer and ALK-positive NSCLC

Country/Region	Incidence (per year)			Source of data
	Annual rate of lung cancer (per 100000)	Number of lung cancer patients	Estimated number of patients with ALK-positive NSCLC***	
Europe	41.9	409911	13937	EUCAN 2012a*
France	49.2	40043	1362	EUCAN 2012a*
Germany	39.8	50813	1728	EUCAN 2012a*
Italy	36.6	37238	1266	EUCAN 2012a*
Spain	43.5	26715	908	EUCAN 2012a*
United Kingdom	45.1	40382	1373	EUCAN 2012a*
US	55.8	222500	7565	SEER (2017)**

*EUCAN incidence rates are age-adjusted to the European standard population;**SEER incidence rates are age-adjusted to the 2000 US population; ***number of ALK-positive NSCLC patients was estimated assuming that 85% of newly diagnosed lung cancer patients have NSCLC and that the frequency of ALK gene rearrangements in patients with NSCLC is 4%.

Prevalence:

The 5-year prevalence of lung cancer, including trachea and bronchus, was 442810 in Europe (40 countries) and 336143 (230842 men and 105301 women) in the EU (27 countries) in 2012 (EUCAN 2012a, EUCAN 2012b, EUCAN 2012c, Bray et al 2013). In the US, there were an estimated 527228 people living with lung and bronchus cancer in 2014 (SEER 2017).

Table 2-2 Prevalence of lung cancer

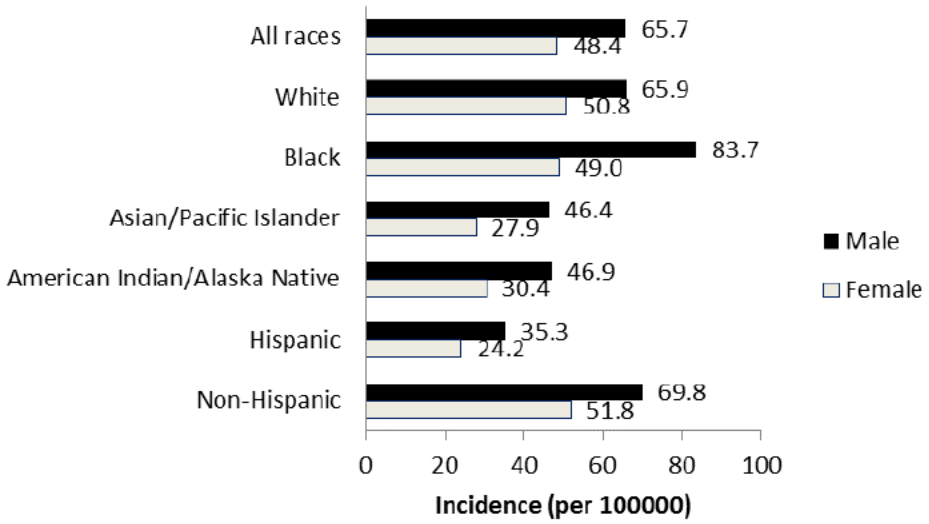
Country/Region	Number of prevalent cases of lung cancer			Source of data/ reference
	1-year	3-year	5-year	EUCAN 2012a
Europe	184032	356582	442810	EUCAN 2012a
France	21863	43732	54811	EUCAN 2012a
Germany	21666	43554	55783	EUCAN 2012a
Italy	17866	35159	43960	EUCAN 2012a
Spain	11551	22532	28148	EUCAN 2012a
United Kingdom	13430	24826	30298	EUCAN 2012a
U.S.A.	103571	210138	268629	GLOBOCAN 2012d

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Lung cancer occurs in men more frequently than women. It is the most common cancer in men worldwide (1.2 million new cases worldwide in 2012, 16.7% of the total). In females, incidence rates are generally lower (583000 cases worldwide in 2012) (GLOBOCAN 2012). According to SEER data in the US, the overall incidence (per 100000) was 65.7 among men and 48.4 among women. The corresponding incidence rates across different races/ethnicities (male

and females) are shown in Figure 2-1 (SEER 2017). The median age at diagnosis of lung cancer of the lung was 70 years in the US.

Figure 2-1 Incidence of lung cancer by race/ethnicity and gender in the US



SEER 18 registries (2010-2014), Age-adjusted rates
Based on SEER Cancer Stat Facts: Lung and Bronchus Cancer (SEER 2017)

Several risk factors contribute to the development of lung cancer, including cigarette, pipe, or cigar smoking; exposure to second-hand smoke, radon, arsenic, asbestos, chromates, chloromethyl ethers, nickel, polycyclic aromatic hydrocarbons, radon progeny, other agents, air pollution; and radiation therapy to the breast or chest (NCI 2013a). Smoking is considered the single most important risk factor for the development of lung cancer.

However, ALK-positive NSCLC has distinct clinical and biologic characteristics, e.g., occurring mainly in non-smokers with adenocarcinoma, younger median age, more commonly female patients and has greater propensity for metastasis (Shaw et al 2009, Kwak et al 2010, Johung et al 2016, Hou et al 2016, Scarpino et al 2016).

The main existing treatment options:

There are different treatment options available for patients with NSCLC (NCI 2013b). These vary depending on the stage of the disease. According to the National Cancer Institute, results of standard treatment in NSCLC are poor except for the most localized cancers. Standard therapy includes surgery, radiation therapy, chemotherapy, targeted therapy, laser therapy, photodynamic therapy, cryosurgery, electrocautery, and watchful waiting (in certain rare cases of NSCLC). Surgery is the most potentially curative therapeutic option and types of surgery include wedge resection, lobectomy, pneumonectomy, and sleeve resection. Postoperative chemotherapy may provide added benefit to patients with resected NSCLC. Radiation therapy in combination with chemotherapy can be curative in some patients and provide palliation in most patients. Prophylactic cranial irradiation may reduce the incidence of brain metastases. In recent years, the identification of mutations in lung cancer, including genetic abnormalities in EGFR, MAPK, and PI3K signaling pathways in subsets of NSCLC, has led to the development

of molecularly targeted therapy to improve the survival of subsets of patients with metastatic disease. Gefitinib, erlotinib, afatinib, and more recently osimertinib for the treatment of NSCLC harboring EGFR mutations or overexpression, and crizotinib, ceritinib and alectinib for the treatment of NSCLC with the anaplastic lymphoma kinase (ALK) fusion translocation oncogenes are examples of targeted approaches to treating cancer (Ma 2012, Yang et al 2012a, Song et al 2015, Tagrisso US Prescribing Information 2015). Standard front-line chemotherapy consists of platinum-based doublets (with or without maintenance), which is generally associated with a poor outcome (response rates of 15 to 35%, median progression-free survival [PFS] of 4 to 7 months and median overall survival [OS] of 8 to 15 months) (NCCN Guidelines v4.2016, Masters et al 2015, Reck et al 2014, Besse et al 2014). Docetaxel and pemetrexed are approved and commonly used as second-line therapies after failure of first-line chemotherapy; the outcome is generally poor with response rates of less than 10%, median PFS of 2 to 3 months, and median OS of 5 to 8 months (Shepherd et al 2000, Fossella et al 2000, Hanna et al 2004, Caponi et al 2010).

Over the past years, ALK-positive NSCLC was demonstrated to respond very well to ALK-inhibitors, and ALK has been validated as the second molecular target in NSCLC after EGFR. Crizotinib (Xalkori®), a first-generation ALK inhibitor, was granted accelerated approval by the Food and Drug Administration (FDA) in August 2011 for the treatment of patients with locally advanced or metastatic ALK-positive NSCLC detected by an FDA approved test. It was also granted conditional marketing authorization in the EU in Oct2012 for the treatment of adults with previously treated ALK-positive advanced NSCLC. Crizotinib converted to regular approval in the US in Nov-2013 based on data from the PROFILE 1007 Study, a randomized Phase III study in patients previously treated with standard platinum-based chemotherapy. In this study, patients with advanced ALK-positive NSCLC whose disease progressed after platinum-based chemotherapy were randomized to receive crizotinib, or docetaxel or pemetrexed. Crizotinib was found to be superior to chemotherapy with regards to median PFS as determined by independent radiologic review (7.7 vs. 3.0 months, respectively, HR=0.49 [95% CI: 0.37, 0.64]; p<0.001) and to ORR (65% vs. 20%, respectively; p<0.001). While pemetrexed performed better than docetaxel, it still remained inferior to crizotinib (median PFS: pemetrexed 4.2 months, docetaxel 2.6 months; ORR: pemetrexed 29%, docetaxel 7%) (Shaw et al 2013). Data from the Phase III study, PROFILE 1014 supported an extension of the indication in the EU for the first-line treatment of adults with ALK-positive advanced NSCLC, the US Prescribing Information (USPI) was updated in Sep-2015 and the SmPC in Nov-2015 based on this study data. While crizotinib is active in patients with ALKpositive NSCLC, these cancers invariably progress, particularly in the central nervous system (CNS), and typically within less than one year, because of the development of resistance to crizotinib. Furthermore, not all patients initially respond to or tolerate crizotinib treatment (Sasaki et al 2011, Doebele et al 2012, Katayama et al 2012, Ou et al 2014).

Upon progression with crizotinib therapy, treatment options include chemotherapy or second-generation ALK inhibitors. While pemetrexed/docetaxel have not been specifically approved for ALK-positive disease, some studies have suggested that pemetrexed may provide higher response rates and longer PFS in patients with ALK-positive NSCLC over other molecular subtypes of lung cancer, thus making it a potential preferred treatment option for patients who failed prior crizotinib (Camidge et al 2011, Lee et al 2011, Lee et al 2013, Shaw et al 2013, Park et al 2016). However, most of these studies were retrospective, and did not include

appropriate controls. The efficacy of pemetrexed and docetaxel after failure of prior chemotherapy and crizotinib needs to be further established. In contrast, ceritinib, the first among the second–generation ALK-inhibitors, has demonstrated robust and durable anti-tumor activity following multiple lines of chemotherapy and crizotinib in Phase I and Phase II studies. Ceritinib was granted accelerated approval in the US in April 2014 for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib, and conditional marketing authorization in the EU in May 2015 for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib. In May 2017, the FDA approved the expanded use of ceritinib to include the first-line treatment of patients with metastatic NSCLC whose tumors are ALK-positive, as detected by an FDA-approved test. In June 2017, the European Commission approved the use of ceritinib for the first-line treatment of patients with advanced NSCLC whose tumors are ALK-positive.

Natural history of the indicated condition in the population, including mortality and morbidity:

In the US, the mortality rates of lung cancer were 55.9 per 100000 men and 36.3 per 100000 women. From 2010-2014, the median age at death for cancer of the lung and bronchus was 72 years of age. The overall 5-year relative survival of patients with lung cancer in the 18 SEER geographic areas from 2007-2013 was 18.1% (SEER 2017).

In a study using a multi-institutional retrospective database of 1521 lung adenocarcinoma patients with brain metastases between 2006 and 2014, the median survival of patients with ALK positive tumors (86 patients) from the first treatment for brain metastases was 45 months (Sperduto et al 2016). Guérin et al (2015) evaluated 119 ALK-positive NSCLC patients who discontinued crizotinib monotherapy. After discontinuing crizotinib monotherapy, 42% had no additional antineoplastic treatment and 13% received radiation therapy only. The median OS post crizotinib monotherapy was 61 days; patients with brain metastases at the time of crizotinib monotherapy discontinuation had shorter OS (44 days) than those who did not (69 days, P=0.018), and patients without further antineoplastic treatment (17 days) had shorter OS than those who did (180 days, P<0.001).The incidence of brain metastases is high in patients with NSCLC, and the brain is frequently the initial site of progression (Yang et al 2012b, Camidge and Doebele 2012). Brain metastases are associated with a high morbidity and poor prognosis (Zhang et al 2015). Emerging data suggest that ALK translocations may increase the risk of developing brain metastases (Yang et al 2012b). Current treatments (whole brain radiation therapy, neurosurgery or stereotactic radiosurgery) are not considered satisfactory for most NSCLC patients with brain metastases, and the prognosis continues to be poor, with a 5-year OS rate of 15% overall (Nguyen et al 2012).

The central nervous system is one of the most common sites of relapse in ALK-positive crizotinib resistant NSCLC patients due to the inability of crizotinib to target CNS lesions (Maillet et al 2013, Solomon et al 2014, Costa et al 2015). The effectiveness of crizotinib in CNS disease is limited by poor blood–brain barrier penetration and acquired drug resistance (Zhang et al 2015).

Other adverse events can occur in patients with advanced or metastatic NSCLC. Patients with lung cancer frequently experience pulmonary infections (Akinosoglou et al 2013). In a study evaluating patients with lung cancer at diagnosis, 33 of 96 patients (34.3%) were found to have

pulmonary infections as determined by quantitative cultures of Broncho alveolar lavage fluid (Putinati et al 1994). In another single centre study of patients with lung cancer, 275 of 442 patients with lung cancer (62.2%) acquired 435 episodes of fever and/or microbiologically or otherwise documented infection over a 4-year period. The majority of the infections occurred in the tracheobronchial tree (56%), including bronchitis (31%), pneumonia (22%) and other pulmonary infections (3%) (Berghmans et al 2003). Post obstructive pneumonia, necrotizing pneumonia and lung abscess are complications of lung cancer occurring in approximately 20% of patients. Postoperative pneumonia represents a common complication following thoracic surgery, ranging from 2% to 25% in patients with lung cancer undergoing pulmonary resection (Akinsouglou et al 2013).

Malignant involvement of the pericardium is known to occur in patients with advanced lung cancer (Barbetakis et al 2010). At autopsy, about 33% of patients with lung cancer are noted to have pericardial metastases (NCI 2013c). Pericardial effusion is common in malignancy, with up to 34% of cancer patients having involvement of pericardium (McCurdy and Shanholtz 2012). According to the Task Force of the European Society of Cardiology on the diagnosis and management of pericardial diseases, 40% of patients with neoplastic pericardial disease have lung cancer (Maisch et al 2004). In a single institution study of patients with cancer who were admitted to the Intensive Care Unit (ICU) with pericardial effusion, lung cancer was the most commonly diagnosed malignancy occurring in 30 of 55 patients in the study (Dequanter et al 2008). In a prospective study of 450 consecutive patients with acute pericardial disease, Imazio et al (2005) noted neoplastic etiology in 33 patients (7.3%) with lung cancer being the most common malignancy.

Important co-morbidities:

Islam et al (2015) evaluated 5683 newly diagnosed lung cancer patients in the U.S. and reported that the most common comorbidities were chronic pulmonary disease (52.5%), diabetes (15.7%), congestive heart failure (12.9%), peripheral vascular disease (8.8%), cerebrovascular disease (7%), myocardial infarction (6.8%) and renal disease (5.7%). Janssen-Heijnen et al (1998) evaluated 3864 lung cancer patients in the Netherlands between 1993 and 1995. The most frequent concomitant diseases reported were cardiovascular diseases (23%), chronic obstructive pulmonary diseases (COPD) (22%), other malignancies (15%), hypertension (12%) and diabetes (7%).

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

The toxicity of ceritinib was evaluated in 2-week non-good laboratory practice (GLP) studies in rats (0, 25 and 100 mg/kg/day) and monkeys (10, 40, and 100 mg/kg/day), 4-week GLP studies in rats (7.5, 25 and 75→50 mg/kg/day) and monkeys (3, 10 and 30 mg/kg/day), 13-week GLP studies in rats and monkeys (3, 10, and 30 mg/kg/day for both species), and a 26-week study in rats (doses 3, 10, and 20 mg/kg/day) and 39-week study in monkeys (doses 3, 10 and 30 mg/kg/day).

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	Relevance to human usage
Gastrointestinal tract (GI) Evidence of GI tract toxicity was observed by body weight loss, decreased food consumption, emesis (monkey), diarrhea, and at high doses, by histopathologic lesions including erosion of the glandular stomach, mucosal inflammation, and foamy macrophages/inflammatory cells in the duodenal crypts and papillae of the small intestine.	The most common adverse events (AEs) in clinical trials with ceritinib have been related to the GI tract (namely nausea, vomiting, diarrhea, and abdominal pain).
Thyroid gland Effects on the thyroid were observed in both rat (mild increases in thyroid stimulating hormone (TSH) and triiodothyronine/thyroxine T3/T4 concentrations with no microscopic correlate) and monkey (depletion of colloid in males in 4-week study, and one monkey at high dose with diffuse follicular cell hyperplasia and increased TSH in 13-week study). As these non-clinical effects were mild, variable, and inconsistent, the relationship between ceritinib and thyroid gland changes in animals is unclear and were also not present in studies up to 39 weeks in duration.	There is no clinical data (AEs, serious adverse events [SAEs]) to support an adverse effect of ceritinib on the thyroid.
Respiratory tract In male rats dosed at 75→50 mg/kg/day for 4 weeks and in rats dosed at 3, 10, and 30 mg/kg for 13 weeks, and in rats dosed at 3, 10, and 20 mg/kg for 26 weeks changes were seen in the lungs (increased incidence of multifocal intra-alveolar foamy macrophage accumulation). Phospholipidosis was confirmed by transmission electron microscopy which revealed the presence of lamellar bodies in the cytoplasm. No evidence of foamy macrophages was seen after recovery. These effects did not translate into functional effects on the respiratory system in a safety pharmacology study in rats. These changes were not observed in monkeys	Relevance of alveolar foamy macrophages in humans remains unknown.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Reproductive toxicity In repeat-dose toxicity studies in rats and monkeys, no adverse effects were observed in male or female reproductive organs. Rat and rabbit embryo fetal studies with ceritinib showed that ceritinib was not fetotoxic and that it did not have teratogenic effects. However, maternal plasma exposure was below those observed at the recommended clinical dose.	Women of childbearing potential should be advised to use a highly effective method of contraception while receiving ceritinib and for up to three months after ending treatment.
Genotoxicity No evidence of genotoxicity has been observed with ceritinib. The Ames assay for ceritinib indicated that it was not a potential mutagen, and the chromosomal aberration assay indicated no evidence of aberrations or clastogenicity. The in vivo genotoxicity study, the rat bone marrow micronucleus assay, has been conducted and the results indicated no effect on the formation of micronuclei in vivo.	The non-clinical data show that there is no potential risk for genotoxicity in humans.
Hepatobiliary system and pancreas In rats and monkeys, repeated doses of ceritinib up to 39 weeks in duration led to changes in the biliary and pancreatic ducts including vacuolation, hypertrophy, inflammation, erosion, necrosis, and hyperplasia. Focal pancreatic atrophy (acinar) and inflammation were also seen, but only in rats at overtly high doses. The changes were mostly mild and reversible. In monkeys, a reversible decrease in zymogen was noted in the acinar pancreas, due to decreased food consumption. No evidence of pancreatic findings was seen in rats and monkeys in the 13-week studies, or in longer term studies in rats (26-week study) and in monkeys (39-week study). Ceritinib led to reversible, moderate increases of aspartate aminotransferase (AST) in rats and monkeys. In non-clinical species, a major route of elimination of ceritinib is via the biliary system. No apparent effect of ceritinib on glucose and insulin levels was evident at any dose tested at repeated doses up to 39 weeks in duration.	In clinical trials elevated transaminases (alanine aminotransferase [ALT] and AST) have been very commonly reported, and in the majority of patients were reversible upon dose modification of ceritinib. Pancreatic enzyme elevations (lipase and/or amylase) and glucose occur in patients treated with ceritinib, In the majority of patients these laboratory abnormalities were reversible upon dose modification of ceritinib. Clinical data suggest that a small proportion (<1%) of patients treated with ceritinib can develop clinical pancreatitis, and the causal role of ceritinib in these cases cannot be excluded.
Blood and lymphatic system In monkeys, at 100 mg/kg/day, drug-related changes in hematology included reduced reticulocytes, mild decreases in bone marrow smear cellularity, and mild decreases in lymphocytes.	In clinical trials anemia has been commonly reported, and decreases in white blood cell counts and platelets have been infrequently reported. The majority of these events were mild, and reversible upon management with additional therapy.
General Pharmacology	
Cardiovascular (including potential for QT interval prolongation)	QT prolongation has been commonly observed in clinical trials with ceritinib.

Key Safety findings (from non-clinical studies)	Relevance to human usage
An in vivo telemetry study in monkeys showed modest QT prolongation in 1 of 4 animals after receiving the highest dose of ceritinib. Electrocardiogram (ECG) studies in monkeys after 4 or 13 weeks of dosing with ceritinib have not shown QT prolongation or abnormal ECGs. A risk was identified in the in vitro hERG assay which showed an inhibitory effect with ceritinib on the hERG channel with an IC50 of 0.4 µM (223 ng/mL free fraction).	No case of Torsades de pointes has been reported.
Central Nervous System and respiratory No effects on the respiratory system or on central nervous system function were observed in rats at doses as high as 100 mg/kg.	Unknown
Mechanisms for drug interactions	
Ceritinib as victim: CYP3A was shown to be the main contributor to the oxidative metabolism of ceritinib based on in vitro studies. Ceritinib was also identified as a substrate of the apical efflux transporter P-glycoprotein (P-gp)**.**	**Ceritinib as victim:** Exposure of ceritinib may therefore be influenced by co-administered agents that affect CYP3A and/or P-gp.
Ceritinib as perpetrator: CYP inhibition studies using human liver microsomes indicated that ceritinib will likely inhibit the in vivo clearance of drugs that are metabolized by CYP2A6, CYP2C9 and CYP3A, and possibly CYP2E1, but not CYP1A2, CYP2B6, CYP2C8, CYP2C19 and CYP2D6.	**Ceritinib as perpetrator:** Based on the assessment of clinical significance of in vitro results using the appropriate drug-drug interaction (DDI) decision tree described in FDA draft DDI guidance 2012 and EMA DDI guideline 2012, only CYP2A6, CYP3A and CYP2C9, and possibly CYP2E1 need to be considered as possible victims of in vivo inhibition by ceritinib. Exposure of medicinal products metabolized by these CYP enzymes may therefore be influenced by co-administration with ceritinib
Other toxicity-related information or data	None

No additional non-clinical studies are necessary.

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

Ceritinib is an orally available, highly potent and selective ALK inhibitor. It inhibits auto phosphorylation of ALK, ALK-mediated phosphorylation of downstream signaling proteins, and proliferation of ALK-dependent cancer cells both in vitro and in vivo. Currently the clinical development program for ceritinib has been focused on a comprehensive evaluation of ceritinib in patients with ALK-positive NSCLC.

This risk management plan contains pooled safety information from the below studies:

- Study LDK378X2101 (hereafter referred to as Study X2101) - A first-in-human, open-label, Phase I, dose-escalation and expansion study of ceritinib in adult patients with tumors confirmed to have genetic abnormalities in ALK. The study comprises a dose-escalation phase to determine the maximum tolerated dose and recommended dose, and an expansion phase in different cohorts of NSCLC patients (i.e., with prior treatment with an ALK inhibitor and with no prior treatment with an ALK inhibitor) and in a cohort of non-lung ALK-positive tumors to better characterize the efficacy, safety and pharmacokinetics (PK) of ceritinib (255 patients received ceritinib 750 mg/day). Data are based on a data cut-off of 03-May-2016.
- Study LDK378X1101 (hereafter referred to as Study X1101) - An open-label, Phase I dose escalation and expansion study conducted in Japanese patients with tumors confirmed to have genetic abnormalities in ALK (eight patients received ceritinib 750 mg/day). Data are based on a data cut-off of 28-Jan-2016.
- Study LDK378A2201 (hereafter referred to as Study A2201) - A Phase II, multicentre, single-arm study of oral ceritinib in adult patients with ALK-activated NSCLC previously treated with chemotherapy and crizotinib (140 patients received ceritinib 750 mg/day). Data are based on the data cut-off of 29-Mar-2016.
- Study LDK378A2203 (hereafter referred to as Study A2203) - A Phase II, multicentre, single-arm study of oral ceritinib in crizotinib naïve adult patients with ALK-activated NSCLC (124 patients received ceritinib 750 mg/day). Data are based on a data cut-off of 15-Nov-2015.
- Study LDK378A2109 (hereafter referred to as Study A2109) - A Phase I/II, multicenter, open-label, single-arm study of ceritinib, administered orally in adult Chinese patients with ALK-positive advanced NSCLC previously treated with crizotinib (103 patients received ceritinib 750 mg/day). Data are based on a data cut-off of 30-Oct-2015.
- Study LDK378A2303 (hereafter referred to as Study A2303) - a Phase III, multicenter, randomized, open-label study of oral ceritinib versus standard chemotherapy (pemetrexed or docetaxel) in adult patients with ALK-positive advanced NSCLC who have been treated previously with chemotherapy (one or two prior regimens, including one platinum doublet) and crizotinib (115 patients received ceritinib 750 mg/day and 113 patients received chemotherapy). Data are based on a data cut-off of 26-Jan-2016.
- Study LDK378A2301 (hereafter referred to as Study A2301) - a Phase III, multicenter, randomized study of oral ceritinib versus standard chemotherapy (pemetrexed plus cisplatin or carboplatin followed by pemetrexed maintenance) in previously untreated adult patients

with ALK-positive stage IIIB or IV, non-squamous NSCLC (189 patients received ceritinib 750 mg/day and 175 patients received chemotherapy). Data are based on a data cut-off of 24-Jun-2016.

Integrated safety analyses were performed by pooling safety data across these seven studies including all NSCLC patients from the ceritinib 750 mg dose group.(N=925).

Table 4-1 Duration of exposure

Duration of Exposure (at least)	Persons	Person months
1 day	925	11932.62
1 week	915	11931.56
12 weeks	774	11736.64
24 weeks	652	11259.50
36 weeks	539	10508.02
48 weeks	453	9706.81
60 weeks	389	8919.52
Summary of exposure (weeks)		
N	925	
Mean (SD)	56.1	
Median	44.9	
Min-Max	0.1-200.1	

- Integrated summary of clinical trial exposure by duration (Safety Set – All patients in the LDK378 750 mg group)
- Data pooled from Study X2101, Study X1101, Study A2201, Study A2203, Study A2109, Study A2303 and Study A2301.
- Person-months=sum (last dose of study drug – first dose of study drug + 1) for all patients / 30.4375

Source: EU RMP v10.0 Annex 12 - Table 4-1p, [SCS Appendix 5 – Table 14.3-1.1]

Table 4-2 Exposure by age group and gender

Age and gender group	Persons	Person months
Male, age <65 years	358	4820.11
Male, age ≥ 65 years	72	830.69
Female, age <65 years	399	5049.03
Female, age ≥ 65 years	96	1232.79
Male	430	5650.79
Female	495	6281.82
Age <65 years	757	9869.14
Age ≥ 65 years	168	2063.47

- Integrated summary of clinical trial exposure by age group and gender (Safety Set – All patients in the LDK378 750 mg group)
- Data pooled from Study X2101, Study X1101, Study A2201, Study A2203, Study A2109, Study A2303 and Study A2301
- Person-months=sum (last dose of study drug – first dose of study drug + 1) for all patients in the gender x age group / 30.4375

Source: EU RMP v10.0 Annex 12 - Table 4-3p

Table 4-3 Exposure by race

Race	Persons	Person months
Caucasian	473	6081.64
Asian	426	5559.26
Black	8	94.78
Other	16	185.86

- Integrated summary of clinical trial exposure by special populations (Safety set – All patients in the LDK378 750 mg group)
- Data pooled from Study X2101, Study X1101, Study A2201, Study A2203, Study A2109, Study A2303 and Study A2301.
- Person-months=sum (last dose of study drug – first dose of study drug + 1) for all patients in the race group / 30.4375

Source EU RMP v10.0 Annex 12 - Table 4-4p

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Patients with unresolved nausea, vomiting or diarrhea >CTCAE grade 1.	1. Nausea, vomiting, and diarrhea are very common toxicities of ceritinib. 2. Precaution to ensure subjects are receiving and absorbing study drug to render an accurate benefit-risk profile.	No	Nausea, vomiting, and diarrhea were the most common AEs associated with ceritinib treatment. The majority of these AEs were grade 1-2, and manageable with study drug adjustment and/or interruption and standards of care including anti-diarrheals, anti-emetics, or fluid replacement, as clinically indicated.
History of pancreatitis or history of increased amylase or lipase that was due to pancreatic disease.	During GLP toxicology studies pancreatic acinar cell atrophy and pancreatic inflammation were observed in rats. Therefore, pancreatitis and amylase/lipase exclusions were added as a precautionary measure.	No	Data for ceritinib shows that lipase/amylase elevations consist mainly in low grade biochemical elevations with no clinical consequences and furthermore, increased amylase has been reported in patients with lung cancer (Tomita et al 1988). Lipase increased and amylase increased are included as commonly reported ADRs in the SmPC. Pancreatitis is included as an uncommon ADR.
Patients using CYP3A substrates with narrow therapeutic indices and that cannot be discontinued at least one week prior to the start of treatment with ceritinib and for the duration of the study. These medicines include, but are not limited	Ceritinib is a reversible and time-dependent CYP3A inhibitor. Exposure of sensitive CYP3A substrates, especially those with narrow therapeutic indices, may be increased when co-administered with ceritinib.	No	The interactions section of the SmPC details the concomitant medications whose exposure may be increased in the presence of ceritinib, and indicates that these drugs should be avoided.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
to alfentanil, astemizole, cisapride, cyclosporine, ergot derivatives, fentanyl pimozide, quinidine, tacrolimus, sirolimus, and terfenadine.			
Patients using CYP2C9 substrates with narrow therapeutic indices and that cannot be discontinued at least one week prior to the start of treatment with ceritinib and for the duration of the study. These medicines include, but are not limited to warfarin, phenytoin.	Ceritinib is a reversible CYP2C9 inhibitor. Exposure of sensitive CYP2C9 substrates, especially those with narrow therapeutic indices, may be increased when co-administered with ceritinib.	No	The interactions section of the SmPC details the concomitant medications whose exposure may be increased in the presence of ceritinib, and indicates that these drugs should be avoided.
Patients using strong inhibitors (including but not limited to clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, posaconazole and voriconazole) or strong inducers (including but not limited to avasimibe, carbamazepine, phenobarbital, phenytoin,	The oxidative metabolism of ceritinib is primarily mediated by CYP3A. Concomitant medications that are strong CYP3A inhibitors may increase the plasma levels of ceritinib, and thus increase the risk of QT prolongation as it has been demonstrated that ceritinib prolonged the QTc interval in a concentration-dependent manner based on population concentration-QTc analyses using a linear mixed effects model (a concentration-QTc	No	The interactions section of the SmPC details the concomitant medications that may increase or decrease the plasma levels of ceritinib, and indicates that these drugs should be avoided.

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
rifabutin, rifampin, and St. John's Wort) of CYP3A and that cannot be discontinued at least one week prior to the start of treatment with ceritinib and for the duration of the study.	response analysis based on the data from Phase III Study A2301 demonstrated that at average steady-state concentrations (C2D1), the mean QTcP change from baseline (416.1 ms) was 13.5 ms (90% CI: 11.8, 15.3) with ceritinib administered at 750 mg daily. Concomitant medications that are strong CYP3A inducers may lower the plasma levels of ceritinib and reduce clinical effectiveness.		
Patients with a prior or current history of interstitial lung disease (ILD).	A case of pneumonitis was initially reported in the clinical development program. The class effect of pneumonitis was also observed with tyrosine kinase inhibitors. Because of these reasons, this was included as an exclusion criterion in the protocols of all the ongoing studies in the ceritinib program.	No	The risk of pneumonitis/ILD is included in the warnings and precautions of the SmPC. As per the SmPC treatment should be permanently discontinued in patients diagnosed with any grade of ILD/pneumonitis.
Clinically significant cardiac disease including congestive heart failure (New York Heart Association Class III or IV), arrhythmia or conduction abnormality requiring medication, or cardiomyopathy; or clinically uncontrolled hypertension (SBP>140 mmHg	Inhibition of the hERG potassium current in an in vitro assay indicated a potential risk for QTc prolongation. Precautionary measure to preclude enrolling patients who might be at risk during assessment of QT risk or may have difficulty permitting interpretation and identification of the occurrence of QT prolongation.	No	Due to lack of data in patients with severe cardiac impairment this patient population was constituted missing information in the RMP. Based on the PRAC recommendation in the assessment report (EMEA/H/C/PSUSA/00010372/201910) received for PSUR 09 (covering period from 29-Oct-2018 to 28-Oct- 2019), considering that there was no additional pharmacovigilance activities for this missing information, it was removed from

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
or DBP>90 mmHg).			list of safety concern of RMP v 16.0.
Serum total bilirubin ≥ 1.5 x upper limit of normal (ULN), except for patients with Gilbert's syndrome who may be included if total bilirubin ≥ 3.0 x ULN and direct bilirubin ≥ 1.5 x ULN. AST and ALT ≥ 2.5 x ULN, except for patients with tumor involvement of the liver who may be included if AST and ALT ≥ 5 x ULN.	Liver laboratory abnormalities are commonly reported with ceritinib.	No	The results of the PK study LDK378A2110 show that the systemic exposure of ceritinib after administration of a single oral 750 mg dose, as assessed by AUC_{inf}, was increased in severe hepatic impairment group by approximately 66% relative to subjects with normal hepatic function, while the systemic exposures in moderate and mild hepatic groups were approximately similar to that of the normal hepatic group. Therefore, safety of ceritinib in this population is not considered as missing information anymore.
Patients with severe renal impairment	Limited data is available as patients with severe renal impairment (CLcr <30 mL/min) were not included in the clinical trial.	No	The totality of (accumulated) scientific and clinical data did not reveal any new safety concern associated with use of ceritinib in patients with severe renal impairment, which needed further characterization. Therefore, this is not considered as missing information.
Pregnant and lactating women, and women of childbearing potential	There are insufficient data regarding the use of Zykadia in pregnant women. The potential risk in humans is unknown. It is unknown whether ceritinib is excreted in human milk. There is a potential for serious adverse drug reactions in breastfed newborns/infants	Yes	This population constitute missing information.

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions due to prolonged exposure, adverse reactions due to cumulative effects and adverse reactions with long latency.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment	• Patients with moderate and severe hepatic impairment were excluded from the studies • Patients with severe renal impairment were excluded from the studies • Patients with severe cardiac impairment were excluded from the studies
Population with relevant different ethnic origin	Not included in the clinical development program.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other Pediatric population	Study CLDK378X2103 (Phase I) in paediatric patients (≤18-year-old) with malignancies carrying a genetic alteration of ALK was completed. Patients enrolled: n=83

Table 5-3 Exposure of special populations included or not in clinical trial development programs (programmed part)

Populations	Persons	Person months
Pregnant women [a]	8	79.24
Renal impairment [b]	408	5275.17
Mild	329	4252.75
Moderate	79	1022.42
Severe	0	0.00
Hepatic impairment [c]	133	1379.12
Mild	132	1374.46
Moderate	1	4.67
Severe	0	0.00

- Integrated summary of clinical trial exposure by special populations (Safety set – All patients in the LDK378 750 mg group)

Populations	Persons	Person months
- Data pooled from Study X2101, Study X1101, Study A2201, Study A2203, Study A2109, Study A2303 and Study A2301.		
- Person-months=sum (last dose of study drug – first dose of study drug + 1) for all patients in the population / 30.4375		
[a] None of the patients had confirmed pregnancy		
[b] Based on the criteria defined in FDA draft renal guidance (2010)		
[c] Based on the NCI-ODWG criteria		
Source: EU RMP v10.0 Annex 12: Table 4-5p		

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

Prescription data was collected from the United States IMS National Prescription Audit database, and the exposure calculation was based on the assumption that each prescription was for a one-month supply.

6.1.2 Part II Module SV.1.2. Exposure

An estimate of the cumulative patient exposure since the IBD was calculated based on the worldwide sales volume in kilogram (kg) of active substance (ceritinib) sold cumulatively up to Oct-2019 and the Defined Daily Dose (DDD) 450 mg and of 750 mg.

The cumulative sales volume amounted to 9,642,847 capsules (approximately 1,446 kg ceritinib free base), corresponding to a cumulative exposure to ceritinib of 6,103 patient treatment years (PTY) (PSUR 29-Oct-2018 to 28-Oct-2019).

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

While no clinical studies have been carried out to specifically investigate abuse potential, no evidence has emerged from clinical trials which would suggest a potential for abuse or dependence. Therefore, the potential for illegal purposes is considered low.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II SVII.1. Identification of safety concerns in the initial RMP submission

8.1.1 Part II SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable; the RMP was already approved.

8.2 Part II SVII.2: New safety concerns and reclassification with a submission of an updated RMP

There was no change in safety concerns since the last update.

8.3 Part II SVII.3: Details of important identified risks, important potential risks, and missing information

8.3.1 SVII.3.1. Presentation of important identified risks and important potential risks

Adverse event, laboratory, and ECG data are presented from the Phase III studies A2301 and A2303 (both the treatment arms – chemotherapy and ceritinib 750 mg/day) and the pooled dataset of patients treated with ceritinib 750 mg/day from the studies - X2101, X1101, A2109, A2201, A2203, A2303, and also A2301.

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

Table 8-1 Clinical trial data

	Study A2110 Hepatic Group				
	Normal N=8 n (%)	**Mild N=9 n (%)**	**Moderate N=10 n (%)**	**Severe N=10 n (%)**	**All Patients N=37 n (%)**
All AEs	4 (50.0)	6 (66.7)	5 (50.0)	6 (60.0)	21 (56.8)
CTC grade 3-4 AEs	0	0	0	2 (20.0)	2 (5.4)
Treatment related AEs	4 (50.0)	5 (55.6)	5 (50.0)	5 (50.0)	19 (51.4)
SAEs	0	0	0	2 (20.0)	2 (5.4)
AEs leading to discontinuation	0	0	0	1 (10.0)	1 (2.7)
AE requiring dose adjustment/ interruption*	0	0	0	0	0
On-treatment deaths	0	0	0	0	0

*Study A2110 was conducted in non-NSCLC patients

N indicates patients enrolled and treated in the study

MedDRA version 19.0 (CompoundCaseRetrievalStrategy_LDK378_MedDRA V19 0_v1) have been used for the reporting of adverse events.

Source: CSR LDK378A2110

Table 8-2 Important potential risk for patients with severe hepatic impairment (including lack of efficacy): other details

Name of the risk: Risk for patients with severe hepatic impairment (including lack of efficacy)	Details
Potential mechanisms	Ceritinib was shown to be highly bound to plasma proteins (>99.2%) in all hepatic groups. Severely impaired hepatic function would result in reduced metabolism and/or reduced biliary excretion of ceritinib following single dose administration.
Evidence source(s) and strength of evidence	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.

Name of the risk: **Risk for patients with severe hepatic impairment (including lack of efficacy)**	Details
	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.
Characterization of the risk:	In Study A2110, the effect of hepatic impairment on the single-dose of ceritinib (750 mg under fasted conditions) was evaluated in patients with mild (Child-Pugh class A; N=8), moderate (Child-Pugh class B; N=7), or severe (Child-Pugh class C; N=7) hepatic impairment and in 8 healthy subjects with normal hepatic function. The geometric mean AUC_{inf} (unbound AUC_{inf}) of ceritinib was increased by 18% (35%) and 2% (22%) in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal hepatic function. The geometric mean AUC_{inf} (unbound AUC_{inf}) of ceritinib was increased by 66% (108%) in subjects with severe hepatic impairment compared to subjects with normal hepatic function. Two subjects had an SAE of grade 3 hepatic encephalopathy; both subjects were in the severe hepatic group and had pre-existing encephalopathy. One of these events was suspected to be related to study drug by the Investigator and led to study discontinuation. The review of all corresponding safety reports did not identify any new safety signal.
Risk factors and risk groups	Patients with severe hepatic impairment
Preventability	When treating patients with severe hepatic impairment, the dose should be reduced by approximately one third, rounded to the nearest multiple of the 150 mg dosage strength
Impact on the benefit-risk balance of the product	The totality of data including a discussion of the results obtained from post-marketing sources is presented in the PSUR up to DLP 28-Oct-2019. The review of all corresponding safety reports did not identify any new safety signal. Moreover, the continued evaluation of ‘Hepatotoxicity’, as an important identified risk in the PSURs, did not identify any history or concurrent condition of hepatic impairment as a risk factor. The impact of this Important potential risk on the overall benefit-risk balance of Zykadia is considered mild due to the lack of evidence of new safety signals in this patient population.
Public health impact	With dose modification and treatment where indicated the public health concern is low.

8.3.2 SVII.3.2. Presentation of the missing information

Table 8-3 Pregnant and lactating women, and women of childbearing potential

Name of missing information Pregnant and lactating women, and women of childbearing potential	**Details**
Evidence source	Reproductive toxicology studies in pregnant rats and rabbits indicated no fetotoxicity or teratogenicity after dosing with ceritinib during organogenesis; however, maternal plasma exposure was less than that observed at the maximum tolerated dose of 750 mg in clinical trials. The potential risk in humans is unknown. Ceritinib should not be given to pregnant women unless the potential benefit outweighs the potential risk to the fetus. Women of childbearing potential should be advised to use a highly effective method of contraception during treatment and for up to three months after ending treatment. It is not known whether ceritinib is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse drug reactions in breast-fed newborns/infants, a decision should be made whether to abstain from breast feeding or abstain from using ceritinib taking into account the importance of ceritinib to the mother.
Anticipated risk/ consequence of the missing information:	The potential for ceritinib to cause infertility in male and female patients is unknown. The information about the safety of ceritinib in pregnancy is very limited.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table Part II SVIII.1: Summary of safety concerns

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

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific follow-up checklist:

A targeted follow-up checklist will be used to further collect baseline data in order to identify patients with severe hepatic impairment. This will help to appropriately characterize and/or closely monitor the important potential risk 'Risk for patients with severe hepatic impairment (including lack of efficacy)'. The checklist is provided in Annex 4.

10.2 Part III.2. Additional pharmacovigilance activities

No additional pharmacovigilance activities are ongoing.

10.3 Part III.3Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study, Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances.				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

11 Part IV: Plans for post-authorization efficacy studies

Table 11-1 Planned and ongoing post-authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations

Not applicable

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

Risk Minimization Plan

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

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important Potential Risks	
Risk for patients with severe hepatic impairment (including lack of efficacy)	**Routine risk communication:** • SmPC Section 4.2 and Section 5.2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • SmPC Section 4.2 Posology and method of administration states that particular caution should be exercised when treating patients with severe hepatic impairment and the dose should be reduced by approximately one third, rounded to the nearest multiple of the 150 mg dosage strength. No dose adjustment is necessary in patients with mild or moderate hepatic impairment. • PK information in SmPC Section 5.2 Pharmacokinetic properties **Other routine risk minimization measures beyond the Product Information:** • Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products'. **Additional risk minimization measures** None
Missing Information	
Pregnant and lactating women, and women of childbearing potential	**Routine risk communication:** • SmPC Section 4.6 and Section 5.3 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Adequate information and guidance to help the prescriber and the patient is provided in Section 4.6 (Fertility, pregnancy, and lactation) of the SmPC. • Preclinical safety data on reproductive toxicology studies (i.e. embryo-foetal development studies) and the potential effects of ceritinib on fertility are detailed in SmPC Section 5.3 (Preclinical safety data). **Other routine risk minimization measures beyond the Product Information:** • Treatment should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.

Safety concern	Routine risk minimization activities
	Additional risk minimization measures • None

12.2 Part V.2. Additional Risk minimization measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

12.3 Part V.3 Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important Potential Risks		
Risk for patients with severe hepatic impairment (including lack of efficacy)	**Routine risk minimization measures** SmPC Sections 4.2, 4.4 and 5.2 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up checklist
Missing Information		
Pregnant and lactating women, and women of childbearing potential	**Routine risk minimization measures** SmPC Section 4.6 and Section 5.3 **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

13 Part VI: Summary of the 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.

13.1 Part VI: 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 (last accessed on 26-Aug-2019).

13.2 Part VI: 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.

13.2.1 Part VI – 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 13-1 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

13.2.2 Part VI - II B: Summary of important risks

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

Table 13-2 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 13-3 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

13.2.3 Part VI – II C: Post-authorization development plan

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

There are no studies that are conditions of the marketing authorization or specific obligation of ceritinib.

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

There are no studies required.

14 Part VII: Annexes

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Annex 4 - Specific adverse drug reaction follow-up forms

Targeted Follow-up Checklist Baseline Information for Patients with Hepatic Impairment/Dysfunction

In addition to collecting routine information for reported adverse events, please ensure the following additional information is provided and/or confirmed regarding the baseline hepatic dysfunction **prior to Zykadia treatment**.

1. **Baseline Liver Function Tests (Please indicate if any additional tests available*)**

Laboratory data	**Baseline worst values (if multiple tests available prior to Zykadia treatment)**		**Normal range**
	Value	**Date**	**(Specify units)**
ALT (GPT)			
AST (GOT)			
ALP			
T-Bil			
D-Bil			
GGT			
LDH			
Other*			

2. **Diagnosis for the hepatic impairment:** ☐ No ☐ Yes

If yes, details_____

Date of diagnosis_____

3. **Other Diagnostic/Laboratory findings at baseline (prior to Zykadia treatment)**

Anti-Hepatitis A virus lgM ☐ No ☐ Yes -- date ( )

Details: _____

Anti-nuclear antibodies (ANA) ☐ No ☐ Yes -- date ( )

Details: _____

Anti -Hepatitis C antibody ☐ No ☐ Yes -- date ( )

Details: _____

Anti-smooth muscle antibodies (ASMA) ☐ No ☐ Yes -- date ( )

Details: _____

Hepatitis B Surface Antigen ☐ No ☐ Yes -- date ( )

Details: _____

Anti-Hepatitis B core antigen lgM □ No □ Yes -- date ( )

Details: _____

Anti-Hepatitis B surface antigen □ No □ Yes -- date ( )

Details: _____

Additional viral serologies (CMV, EBV) □ No □ Yes -- date ( )

Details: _____

Coagulation parameter □ No □ Yes -- date ( )

Details: _____

Eosinophil count □ No □ Yes -- date ( )

Details: _____

Abdominal Ultrasound □ No □ Yes -- date ( )

Details: _____

Computed Tomography (CT) □ No □ Yes -- date ( )

Details: _____

Endoscopic Retrograde

Cholangio Pancreatography (ERCP) □ No □ Yes -- date ( )

Details: _____

Liver Biopsy □ No □ Yes -- date ( )

Details: _____

□ Other_____

*Please attach to summarize available results

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Not applicable