ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Zykadia 150 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 150 mg ceritinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Capsule with white opaque body and blue opaque cap, with "LDK 150MG" imprinted on the cap and "NVR" on the body, containing white to almost white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zykadia 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.

4.2 Posology and method of administration

Treatment with Zykadia should be initiated and supervised by a physician experienced in the use of anti-cancer medicinal products.

ALK testing

An accurate and validated ALK assay is necessary for the selection of ALK-positive NSCLC patients (see section 5.1).

ALK-positive NSCLC status should be established prior to initiation of Zykadia therapy. Assessment for ALK-positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilised.

Posology

The recommended dose of Zykadia is 750 mg taken orally once daily at the same time each day.

The maximum recommended dose is 750 mg daily. Treatment should continue as long as clinical benefit is observed.

If a dose is missed, the patient should make up that dose, unless the next dose is due within 12 hours.

Zykadia should be discontinued in patients unable to tolerate 300 mg daily.

Dose adjustment due to adverse reactions
Temporary dose interruption and/or dose reduction of Zykadia may be required based on individual safety and tolerability. If dose reduction is required due to any adverse drug reaction (ADR), then this should be achieved by decrements of 150 mg daily. Early identification and management of ADRs with standard supportive care measures should be considered.

Approximately 54% of patients initiating treatment at the recommended dose of 750 mg required at least one dose adjustment due to adverse reaction, with a median time to first dose reduction of approximately 7 weeks.

Table 1 summarises recommendations for dose interruption, reduction or discontinuation of Zykadia in the management of selected ADRs.

Table 1 Zykadia dose adjustment and management recommendations for ADRs

Criteria	**Zykadia dosing**
Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation >5 times upper limit of normal (ULN) with total bilirubin ≤2 times ULN	Withhold Zykadia until recovery to baseline or ≤3 times ULN, then reinitiate with dose reduced by one decrement.
ALT or AST elevation >3 times ULN with concurrent total bilirubin elevation >2 times ULN (in the absence of cholestasis or haemolysis)	Permanently discontinue Zykadia.
Any grade treatment-related pneumonitis	Permanently discontinue Zykadia.
QT corrected for heart rate (QTc) >500 msec on at least 2 separate electrocardiograms (ECGs)	Withhold Zykadia until recovery to baseline or to a QTc ≤480 msec, check and if necessary correct electrolytes, then reinitiate with dose reduced by one decrement.
QTc >500 msec or >60 msec change from baseline and torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue Zykadia.
Bradycardia[a] (symptomatic, may be severe and medically significant, medical intervention indicated)	Withhold Zykadia until recovery to asymptomatic (grade ≤1) bradycardia or to a heart rate of 60 beats per minute (bpm) or above. Evaluate concomitant medicinal products known to cause bradycardia, as well as anti-hypertensive medicinal products. If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, reinitiate Zykadia at the previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If no contributing concomitant medicinal product is identified, or if contributing concomitant medicinal products are not discontinued or dose modified, reinitiate Zykadia with dose reduced by one decrement upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above.

Bradycardia[a] (life-threatening consequences, urgent intervention indicated)	Permanently discontinue Zykadia if no contributing concomitant medicinal product is identified. If a contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, reinitiate Zykadia with dose reduced by two decrements upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring[b].
Severe (grade 3) or intolerable nausea, vomiting or diarrhoea despite optimal anti-emetic or anti-diarrhoeal therapy	Withhold Zykadia until improved, then reinitiate Zykadia with dose reduced by one decrement.
Persistent hyperglycaemia greater than 250 mg/dl despite optimal anti-hyperglycaemic therapy	Withhold Zykadia until hyperglycaemia is adequately controlled, then reinitiate Zykadia with dose reduced by one decrement. If adequate glucose control cannot be achieved with optimal medical management, permanently discontinue Zykadia.
Lipase or amylase elevation grade ≥3	Withhold Zykadia until lipase or amylase returns to grade ≤1, then reinitiate with dose reduced by one decrement.
[a] Heart rate less than 60 beats per minutes (bpm) [b] Permanently discontinue in the event of recurrence.	

Avoid concomitant use of strong CYP3A inhibitors during treatment with Zykadia (see section 4.5). If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the dose by approximately one third (dose not clinically verified), rounded to the nearest multiple of the 150 mg dosage strength. Patients should be carefully monitored for safety.

If long-term concomitant treatment with a strong CYP3A inhibitor is necessary and the patient tolerates the reduced dose well, the dose may be increased again with careful monitoring for safety, to avoid potential under-treatment.

After discontinuation of a strong CYP3A inhibitor, resume at the dose that was taken prior to initiating the strong CYP3A inhibitor.

Special populations

Renal impairment
A dedicated pharmacokinetic study in patients with renal impairment has not been conducted. However, based on available data, ceritinib elimination via the kidney is negligible. Therefore, no dose adjustment is necessary in patients with mild to moderate renal impairment. Caution should be used in patients with severe renal impairment as there is no experience with ceritinib in this population (see section 5.2).

Hepatic impairment
A dedicated pharmacokinetic study in patients with hepatic impairment has not been conducted. Based on available data, ceritinib is eliminated primarily via the liver. No dose adjustment is necessary in patients with mild hepatic impairment. Ceritinib is not recommended in patients with moderate to severe hepatic impairment (see section 5.2).

Elderly (≥65 years)
The limited data on the safety and efficacy of ceritinib in patients aged 65 years and older do not suggest that a dose adjustment is required in elderly patients (see section 5.2). There are no available data on patients over 85 years of age.

Paediatric population
The safety and efficacy of ceritinib in children and adolescents aged up to 18 years have not been established. No data are available.

Method of administration

Zykadia is for oral use. The capsules should be administered orally once daily at the same time every day. They should be swallowed whole with water and should not be chewed or crushed. The capsules must be taken on an empty stomach and no food should be eaten for at least two hours before and two hours after the dose is taken (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hepatotoxicity

Cases of hepatotoxicity occurred in less than 1% of patients receiving ceritinib in clinical studies. Increases to grade 3 or 4 ALT elevations were observed in 25% of patients. The majority of cases were manageable with dose interruption and/or dose reduction. Few events required discontinuation of treatment.

Patients should be monitored with liver laboratory tests (including ALT, AST and total bilirubin) prior to the start of treatment, every 2 weeks for the first month of treatment and monthly thereafter. In patients who develop transaminase elevations, more frequent monitoring of liver transaminases and total bilirubin should be carried out as clinically indicated (see sections 4.2 and 4.8). Ceritinib is not recommended for patients with moderate to severe hepatic impairment (see sections 4.2 and 4.8).

Interstitial lung disease / Pneumonitis

Severe, life-threatening or fatal interstitial lung disease (ILD) / pneumonitis have been observed in patients treated with ceritinib in clinical studies. Most cases improved or resolved with interruption of treatment.

Patients should be monitored for pulmonary symptoms indicative of pneumonitis. Other potential causes of pneumonitis should be excluded, and Zykadia permanently discontinued in patients diagnosed with treatment-related pneumonitis (see sections 4.2 and 4.8).

QT interval prolongation

QTc prolongation has been observed in clinical studies in patients treated with ceritinib (see sections 4.8 and 5.2), which may lead to an increased risk for ventricular tachyarrhythmias (e.g. torsade de pointes) or sudden death.

Use of Zykadia in patients with congenital long QT syndrome should be avoided. The benefits and potential risks of ceritinib should be considered before beginning therapy in patients who have pre-existing bradycardia (heart rate less than 60 beats per minute [bpm]), patients who have a history of or predisposition for QTc prolongation, patients who are taking anti-arrhythmics or other medicinal products that are known to prolong the QT interval and patients with relevant pre-existing cardiac disease and/or electrolyte disturbances. Periodic monitoring with ECGs and periodic monitoring of electrolytes (e.g. potassium) is recommended in these patients. In the event of vomiting, diarrhoea, dehydration or impaired renal function, correct electrolytes as clinically indicated. Zykadia should be permanently discontinued in patients who develop QTc >500 msec or >60 msec change from baseline and torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. Zykadia should be withheld in patients who develop QTc >500 msec on at least two separate ECGs until recovery to baseline or a QTc ≤480 msec, then reinitiated with dose reduced by one decrement (see sections 4.2, 4.8 and 5.2).

Bradycardia

Asymptomatic cases of bradycardia (heart rate less than 60 bpm) have been observed in 10 out of 525 (1.9%) patients treated with ceritinib in clinical studies.

Use of Zykadia in combination with other agents known to cause bradycardia (e.g. beta blockers, non-dihydropyridine calcium channel blockers, clonidine and digoxin) should be avoided as far as possible. Heart rate and blood pressure should be monitored regularly. In cases of symptomatic bradycardia that is not life-threatening, Zykadia should be withheld until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, the use of concomitant medicinal products should be evaluated and the Zykadia dose adjusted if necessary. In the event of life-threatening bradycardia Zykadia should be permanently discontinued if no contributing concomitant medicinal product is identified; however, if associated with a concomitant medicinal product known to cause bradycardia or hypotension, Zykadia should be withheld until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If the concomitant medicinal product can be adjusted or discontinued, Zykadia should be reinitiated with dose reduced by two decrements on recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring (see sections 4.2 and 4.8).

Gastrointestinal toxicity

In clinical studies with ceritinib, diarrhoea, nausea and vomiting have been very commonly reported; grade 3-4 events of diarrhoea, nausea or vomiting were reported in 12.2% of patients.

Patients should be monitored and managed using standards of care, including anti-diarrhoeals, anti-emetics or fluid replacement, as clinically indicated. Dose interruption and dose reduction should be employed as necessary (see sections 4.2 and 4.8). If vomiting occurs during the course of treatment, the patient should not take an additional dose, but should continue with the next scheduled dose.

Hyperglycaemia

Cases of hyperglycaemia (all grades) have been reported in less than 10% of patients treated with ceritinib in clinical studies; grade 3-4 hyperglycaemia was reported in 5% of patients. The risk of hyperglycaemia was higher in patients with diabetes mellitus and/or concurrent steroid use.

Patients should be monitored for fasting plasma glucose prior to the start of Zykadia treatment and periodically thereafter as clinically indicated. Anti-hyperglycaemic medicinal products should be initiated or optimised as indicated (see sections 4.2 and 4.8).

Lipase and/or amylase elevations

Elevations of lipase and/or amylase have occurred in patients treated with ceritinib in clinical studies. Patients should be monitored for lipase and amylase elevations prior to the start of Zykadia treatment and periodically thereafter as clinically indicated (see sections 4.2 and 4.8). Cases of pancreatitis have been reported in patients treated with ceritinib (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Agents that may increase ceritinib plasma concentrations

In healthy subjects, co-administration of a single 450 mg ceritinib dose with ketoconazole (200 mg twice daily for 14 days), a strong CYP3A/P-gp inhibitor, resulted in 2.9-fold and 1.2-fold increase in ceritinib AUC_{inf} and C_{max}, respectively, compared to when ceritinib was given alone. The steady-state AUC of ceritinib at reduced doses after co-administration with ketoconazole 200 mg twice daily for 14 days was predicted by simulations to be similar to the steady-state AUC of ceritinib alone. If it is not possible to avoid concomitant use with strong CYP3A inhibitors (including, but not limited to, ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole and nefazodone), reduce the ceritinib dose by approximately one third, rounded to the nearest multiple of the 150 mg dosage strength. After discontinuation of a strong CYP3A inhibitor, resume the ceritinib dose that was taken prior to initiating the strong CYP3A inhibitor.

Based on *in vitro* data, ceritinib is a substrate of the efflux transporter P-glycoprotein (P-gp). If ceritinib is administered with medicinal products that inhibit P-gp, an increase in ceritinib concentration is likely. Caution should be exercised with concomitant use of P-gp inhibitors and ADRs carefully monitored.

Agents that may decrease ceritinib plasma concentrations

In healthy subjects, co-administration of a single 750 mg ceritinib dose with rifampicin (600 mg daily for 14 days), a strong CYP3A/P-gp inducer, resulted in 70% and 44% decreases in ceritinib AUC_{inf} and C_{max}, respectively, compared to when ceritinib was given alone. Co-administration of ceritinib with strong CYP3A/P-gp inducers decreases ceritinib plasma concentrations. Concomitant use of strong CYP3A inducers should be avoided; this includes, but is not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St. John's Wort (*Hypericum perforatum*). Caution should be exercised with concomitant use of P-gp inducers.

Ceritinib demonstrates pH-dependent solubility and becomes poorly soluble as pH increases *in vitro*. Acid reducing agents (e.g., proton pump inhibitors, H_2-receptor antagonists, antacids) can alter the solubility of ceritinib and reduce its bioavailability. Co-administration of a single 750 mg ceritinib dose with a proton pump inhibitor (esomeprazole) 40 mg daily for 6 days in healthy, fasting subjects decreased ceritinib AUC by 76% and C_{max} by 79%. A dedicated study to evaluate the effect of gastric acid-reducing agents on the bioavailability of ceritinib under steady state has not been conducted. Caution is advised with concomitant use of proton pump inhibitors, as exposure of ceritinib may be reduced. There is no data with concomitant use of H_2 blockers or antacids. However, the risk for a clinically relevant decrease in bioavailability of ceritinib is possibly lower with concomitant use of H_2 blockers if they are administered 10 hours before or 2 hours after the ceritinib dose, and with antacids if they are administered 2 hours before or 2 hours after the ceritinib dose.

Agents whose plasma concentration may be altered by ceritinib

Based on *in vitro* data, ceritinib competitively inhibits the metabolism of a CYP3A substrate, midazolam, and a CYP2C9 substrate, diclofenac. Time-dependent inhibition of CYP3A was also observed. The steady-state C_{max} value of ceritinib at the recommended clinical dose of 750 mg daily may exceed the Ki values for CYP3A and CYP2C9, suggesting that ceritinib could inhibit the clearance of other medicinal products metabolised by these enzymes at clinically relevant concentrations. Dose reduction may be needed for co-administered medicinal products that are predominantly metabolised by CYP3A and CYP2C9. Co-administration of ceritinib with CYP3A substrates known to have narrow therapeutic indices (e.g. astemizole, cisapride, ciclosporin, ergotamine, fentanyl, pimozide, quinidine, tacrolimus, alfentanil and sirolimus) and CYP2C9 substrates known to have narrow therapeutic indices (e.g. phenytoin and warfarin) should be avoided.

Based on *in vitro* data, ceritinib also inhibits CYP2A6 and CYP2E1 at clinically relevant concentrations. Therefore, ceritinib may have the potential to increase plasma concentrations of co-administered medicinal products that are predominantly metabolised by these enzymes. Caution should be exercised with concomitant use of CYP2A6 and CYP2E1 substrates and ADRs carefully monitored.

A risk for induction of other PXR regulated enzymes apart from CYP3A4 cannot be completely excluded. The effectiveness of concomitant administration of oral contraceptives may be reduced.

Agents that are substrates of transporters

Based on *in vitro* data, ceritinib does not inhibit apical efflux transporter MRP2, hepatic uptake transporters OATP1B1 or OATP1B3, renal organic anion uptake transporters OAT1 and OAT3, or the organic cation uptake transporters OCT1 or OCT2 at clinically relevant concentrations. Therefore, clinical drug-drug interactions as a result of ceritinib-mediated inhibition of substrates for these transporters are unlikely to occur. Based on *in vitro* data, ceritinib is predicted to inhibit intestinal P-gp and BCRP at clinically relevant concentrations. Therefore, ceritinib may have the potential to increase plasma concentrations of co-administered medicinal products transported by these proteins. Caution should be exercised with concomitant use of BCRP substrates (e.g. rosuvastatin, topotecan, sulfasalazine) and P-gp substrates (digoxin, dabigatran, colchicine, pravastatin) and ADRs carefully monitored.

Pharmacodynamic interactions

In clinical studies, QT prolongation was observed with ceritinib. Therefore, ceritinib should be used with caution in patients who have or may develop prolongation of the QT interval, including those patients taking anti-arrhythmic medicinal products such as class I (e.g. quinidine, procainamide, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) anti-arrhythmics or other medicinal products that may lead to QT prolongation such as astemizole, domperidone, droperidol, chloroquine, halofantrine, clarithromycin, haloperidol, methadone, cisapride and moxifloxacin. Monitoring of the QT interval is indicated in the event of combinations of such medicinal products (see sections 4.2 and 4.4).

Food/drink interactions

The bioavailability of ceritinib is increased in the presence of food depending on the fat content in the meal (see section 5.2). Ceritinib should be taken on an empty stomach. No food should be eaten for at least two hours before and two hours after the dose is taken.

Patients should be instructed to avoid grapefruit and grapefruit juice as they may inhibit CYP3A in the gut wall and may increase the bioavailability of ceritinib.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to use a highly effective method of contraception while taking Zykadia and for up to 3 months after discontinuing treatment (see section 4.5).

Pregnancy

There are no or limited amount of data from the use of ceritinib in pregnant women.

Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

Zykadia should not be used during pregnancy unless the clinical condition of the woman requires treatment with ceritinib.

Breast-feeding

It is unknown whether ceritinib/metabolites are excreted in human milk. A risk to the newborn/infant cannot be excluded.

A decision must be made whether to discontinue breast-feeding or discontinue/abstain from Zykadia therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman (see section 5.3).

Fertility

The potential for Zykadia to cause infertility in male and female patients is unknown (see section 5.3).

4.7 Effects on ability to drive and use machines

Zykadia has minor influence on the ability to drive or use machines. Caution should be exercised when driving or using machines during treatment as patients may experience fatigue or vision disorders.

4.8 Undesirable effects

Summary of the safety profile

The data described below reflect exposure to Zykadia in 525 patients with tumours confirmed to have genetic abnormalities in ALK (515 ALK-positive NSCLC patients and 10 non-NSCLC patients) and treated at the dose of 750 mg in four open-label, single-arm clinical studies.

The median duration of exposure to Zykadia was 33.0 weeks (range: 0.3 to 106.1 weeks).

ADRs with an incidence of ≥10% were diarrhoea, nausea, vomiting, fatigue, liver laboratory test abnormalities, abdominal pain, decreased appetite, constipation, rash, blood creatinine increased, oesophageal disorder and anaemia.

Grade 3-4 ADRs with an incidence of ≥5% were liver laboratory test abnormalities, fatigue, diarrhoea, nausea and hyperglycaemia.

Tabulated list of ADRs

Table 2 shows the frequency category of ADRs reported for Zykadia in patients treated at the starting dose of 750 mg in four clinical studies.

ADRs are listed according to MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each ADR: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available data).

Table 2 ADRs in patients treated with Zykadia at a dose of 750 mg

System organ class Preferred term	Zykadia N=525 %	Frequency category
Blood and lymphatic system disorders		
Anaemia	11.4	Very common
Metabolism and nutrition disorders		
Decreased appetite	41.1	Very common
Hyperglycaemia	7.8	Common
Hypophosphataemia	5.3	Common
Eye disorders		
Vision disorder[a]	7.4	Common
Cardiac disorders		
Pericarditis[b]	5.9	Common
Bradycardia[c]	1.9	Common
Respiratory, thoracic and mediastinal disorders		
Pneumonitis[d]	3.2	Common
Gastrointestinal disorders		
Diarrhoea	83.8	Very common
Nausea	79.8	Very common
Vomiting	62.9	Very common
Abdominal pain[e]	48.2	Very common
Constipation	25.1	Very common
Oesophageal disorder[f]	15.0	Very common
Pancreatitis	0.4	Uncommon
Hepatobiliary disorders		
Abnormal liver function tests[g]	2.1	Common
Hepatotoxicity[h]	0.6	Uncommon
Skin and subcutaneous tissue disorders		
Rash[i]	19.0	Very common
Renal and urinary disorders		
Renal failure[j]	2.1	Common
Renal impairment[k]	1.3	Common
General disorders and administration site conditions		
Fatigue[l]	50.5	Very common

Investigations		
Liver laboratory test abnormalities[m]	50.5	Very common
Blood creatinine increased	17.7	Very common
Electrocardiogram QT prolonged	6.5	Common
Lipase increased	4.6	Common
Amylase increased	4.6	Common

Includes cases reported within the clustered terms:

[a] Vision disorder (vision impairment, vision blurred, photopsia, vitreous floaters, visual acuity reduced, accommodation disorder, presbyopia)
[b] Pericarditis (pericardial effusion, pericarditis)
[c] Bradycardia (bradycardia, sinus bradycardia)
[d] Pneumonitis (interstitial lung disease, pneumonitis)
[e] Abdominal pain (abdominal pain, abdominal pain upper, abdominal discomfort, epigastric discomfort)
[f] Oesophageal disorder (dyspepsia, gastro-oesophageal reflux disease, dysphagia)
[g] Abnormal liver function test (hepatic function abnormal, hyperbilirubinaemia)
[h] Hepatotoxicity (drug-induced liver injury, hepatitis cholestatic, hepatocellular injury, hepatotoxicity)
[i] Rash (rash, dermatitis acneiform, rash maculopapular)
[j] Renal failure (renal failure acute, renal failure)
[k] Renal impairment (azotaemia, renal impairment)
[l] Fatigue (fatigue, asthenia)
[m] Liver laboratory test abnormalities (alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood bilirubin increased, transaminases increased, hepatic enzyme increased, liver function test abnormal)

Elderly (≥65 years)

Across four clinical studies, 89 out of 525 patients (17.0%) treated with Zykadia were aged 65 years or older. The safety profile in patients aged 65 years or older was similar to that in patients less than 65 years of age (see section 4.2). There are no safety data in patients older than 85 years of age.

Hepatotoxicity

Concurrent elevations of ALT greater than 3× ULN and total bilirubin greater than 2× ULN without elevated alkaline phosphatase have been observed in less than 1% of patients in clinical studies with ceritinib. Increases to grade 3 or 4 ALT elevations were observed in 25% of patients receiving ceritinib. Hepatotoxicity events were managed with dose interruptions or reductions in 34.3% of patients. Less than 1% of patients required permanent discontinuation of treatment in clinical studies with ceritinib (see section 4.4). Ceritinib is not recommended in patients with moderate or severe hepatic impairment (see section 4.2).

Liver laboratory tests including ALT, AST and total bilirubin should be performed prior to the start of treatment, every 2 weeks for the first month and monthly thereafter, with more frequent testing for grade 2, 3 or 4 elevations. Patients should be monitored for liver laboratory test abnormalities and managed as recommended in sections 4.2 and 4.4.

Gastrointestinal effects

Nausea, diarrhoea and vomiting were the most commonly reported gastrointestinal events. Grade 3 or 4 events of diarrhoea, nausea or vomiting were reported in 12.2% of patients. Gastrointestinal events were managed primarily with concomitant medicinal products including anti-emetic/anti-diarrhoeal medicinal products (in 84.8% of patients) and/or with dose reduction or interruption (in 33.0% of patients). Gastrointestinal events led to discontinuation in 0.6% of patients. Patients should be managed as recommended in sections 4.2 and 4.4.

QT interval prolongation

QTc prolongation has been observed in patients treated with ceritinib. Across the four clinical studies, 6.5% of patients treated with ceritinib had events of QT prolongation (any grade), including grade 3 or 4 events in 0.8% of patients. These events required dose reduction or interruption in 1% of patients and led to discontinuation in 0.2% of patients.

Treatment with ceritinib is not recommended in patients who have congenital long QT syndrome or who are taking medicinal products known to prolong the QTc interval (see sections 4.4 and 4.5). Particular care should be exercised when administering ceritinib to patients with an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging medicinal product.

Patients should be monitored for QT prolongation and managed as recommended in sections 4.2 and 4.4.

Bradycardia

Across the four clinical studies, bradycardia and/or sinus bradycardia (heart rate less than 60 bpm) events (all grade 1) were reported in 1.9% of patients. None of these events led to dose reduction or interruption or to discontinuation of ceritinib treatment. The use of concomitant medicinal products associated with bradycardia should be carefully evaluated. Patients who develop symptomatic bradycardia should be managed as recommended in sections 4.2 and 4.4.

Interstitial lung disease / Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD) / pneumonitis have been observed in patients treated with ceritinib. Across the four clinical studies, any grade ILD/pneumonitis has been reported in 3.2% of patients treated with ceritinib, and grade 3 or 4 events have been reported in 1.9% of patients. These events required dose reduction or interruption in 1.9% of patients and led to discontinuation in 1.1% of patients. Patients with pulmonary symptoms indicative of ILD/pneumonitis should be monitored. Other potential causes of ILD/pneumonitis should be excluded (see sections 4.2 and 4.4).

Hyperglycaemia

Hyperglycaemia (all grades) was reported in 7.8% of patients treated with ceritinib across the four clinical studies; grade 3 or 4 events were reported in 5.0% of patients. These events required dose reduction or interruption in 1.3% of patients and led to discontinuation in 0.2% of patients. The risk of hyperglycaemia was higher in patients with diabetes mellitus and/or concurrent steroid use. Monitoring of fasting serum glucose is required prior to the start of ceritinib treatment and periodically thereafter as clinically indicated. Administration of anti-hyperglycaemic medicinal products should be initiated or optimised as indicated (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no reported experience with overdose in humans. General supportive measures should be initiated in all cases of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplasic and immunomodulating agents, ATC code: L01XE28.

Mechanism of action

Ceritinib is an orally highly selective and potent ALK inhibitor. Ceritinib inhibits autophosphorylation of ALK, ALK-mediated phosphorylation of downstream signalling proteins and proliferation of ALK-dependent cancer cells both *in vitro* and *in vivo*.

ALK translocation determines expression of the resulting fusion protein and consequent aberrant ALK signaling in NSCLC. In the majority of NSCLC cases, EML4 is the translocation partner for ALK; this generates an EML4-ALK fusion protein containing the protein kinase domain of ALK fused to the N-terminal part of EML4. Ceritinib was demonstrated to be effective against EML4-ALK activity in a NSCLC cell line (H2228), resulting in inhibition of cell proliferation *in vitro* and regression of tumours in H2228-derived xenografts in mouse and rat.

Clinical efficacy and safety

The use of Zykadia in the treatment of ALK-positive NSCLC patients previously treated with an ALK inhibitor was investigated in two global, multicentre, open-label, single-arm studies (Study A and Study B). Comparative efficacy data from randomised clinical studies are not yet available.

The primary efficacy endpoint for these studies was overall response rate (ORR), defined as the proportion of patients with best response of complete response (CR) or partial response (PR) confirmed by repeat assessments performed not less than 4 weeks after the criteria for response was first met. Additional evaluations included duration of response (DOR) and progression-free survival (PFS) by investigator and blinded independent review committee (BIRC) assessment, and overall survival (OS). Tumour evaluations were performed according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 in Study A and RECIST 1.1 in Study B.

Study A was a phase 1 study which included a dose-escalation phase and an expansion phase, at the recommended dose of 750 mg. All patients enrolled in the study had locally advanced or metastatic malignancy that had progressed despite standard therapy. A total of 246 ALK-positive NSCLC patients were enrolled who were treated at a Zykadia dose of 750 mg: 163 who had received prior treatment with an ALK inhibitor and 83 who were ALK inhibitor naïve.

Of the 163 ALK-positive NSCLC patients who had received prior treatment with an ALK inhibitor, the median age was 52 years (range: 24-80 years); 86.5% of patients were younger than 65 years. A total of 54% of patients were female. The majority of patients were Caucasian (66.3%) or Asian (28.8%). The vast majority of patients had adenocarcinoma (93.3%) and had either never been or were former smokers (96.9%). All of the patients were treated with at least one regimen prior to enrolment into the study, 16.0% with one prior regimen, and 84% with two or more regimens.

Study B was a phase 2 study to evaluate the efficacy and safety of 750 mg ceritinib in patients with locally advanced or metastatic ALK-positive NSCLC. Study B involved 140 patients who had been previously treated with 1-3 lines of cytotoxic chemotherapy followed by treatment with crizotinib, and who had then progressed on crizotinib.

In Study B, the median age was 51 years (range: 29-80 years); 87.1% of patients were younger than 65 years. A total of 50.0% of patients were female. The majority of patients were Caucasian (60.0%) or Asian (37.9%). The vast majority of patients had adenocarcinoma (92.1%).

Main efficacy results from Studies A and B

The main efficacy data for both studies are summarised in Table 3. Final overall survival (OS) data are presented for Study B. For Study A, OS data were not yet mature at the time of the analysis.

Table 3 ALK-positive advanced NSCLC - overview of efficacy results from Studies A and B

	Study A ceritinib 750 mg N=163	Study B ceritinib 750 mg N=140
Duration of follow-up	10.2	14.1
Median (months) (min – max)	(0.1 – 24.1)	(0.1 – 35.5)
Overall response rate		
Investigator		
n (%)	92 (56.4)	57 (40.7)
(95% CI)	(48.5, 64.2)	(32.5, 49.3)
BIRC		
n (%)	75 (46.0)	50 (35.7)
(95% CI)	(38.2, 54.0)	(27.8, 44.2)
Duration of response*		
Investigator		
Median (months)	8.3	10.6
(95% CI)	(6.8, 9.7)	(7.4, 14.7)
BIRC		
Median (months)	8.8	12.9
(95% CI)	(6.0, 13.1)	(9.3, 18.4)
Progression-free survival		
Investigator		
Median (months)	6.9	5.8
(95% CI)	(5.6, 8.7)	(5.4, 7.6)
BIRC		
Median (months)	7.0	7.4
(95% CI)	(5.7, 8.6)	(5.6, 10.9)
Overall survival		
Median (months)	16.7	15.6
(95% CI)	(14.8, NE)	(13.6, 24.2)

NE = not estimable
Study A: Responses assessed using RECIST 1.0
Study B: Responses assessed using RECIST 1.1
*Includes only patients with confirmed CR, PR

Patients with brain metastases

In Studies A and B, brain metastases were seen in 60.1% and 71.4% of patients, respectively. The ORR, DOR and PFS (by BIRC assessment) for patients with brain metastases at baseline were in line with those reported for the overall population of these studies.

Non-adenocarcinoma histology

Limited information is available in ALK-positive NSCLC patients with non-adenocarcinoma histology.

Elderly

Limited efficacy data are available in elderly patients. No efficacy data are available in patients over 85 years of age.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Zykadia in all subsets of the paediatric population in lung carcinoma (small cell and non-small cell carcinoma) (see section 4.2 for information on paediatric use).

Conditional approval

This medical product has been authorised under a so-called "conditional approval" scheme. This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption

Peak plasma levels (C_{max}) of ceritinib are achieved approximately 4 to 6 hours after oral administration in patients. Oral absorption was estimated to be ≥25% based on metabolite percentages in the faeces. The absolute bioavailability of ceritinib has not been determined.

Systemic exposure to ceritinib is increased when administered with food. Ceritinib AUC_{inf} values were approximately 58% and 73% higher (C_{max} approximately 43% and 41% higher) when administered with a low fat meal and a high fat meal, respectively.

After single oral administration of ceritinib in patients, plasma exposure to ceritinib, as represented by C_{max} and AUC_{last}, increased dose-proportionally over the 50 to 750 mg dose range. In contrast with single-dose data, pre-dose concentration (C_{min}) after repeated daily dosing appeared to increase in a greater than dose-proportional manner.

Distribution

Binding of ceritinib to human plasma proteins *in vitro* is approximately 97% in a concentration independent manner, from 50 ng/ml to 10,000 ng/ml. Ceritinib also has a slight preferential distribution to red blood cells, relative to plasma, with a mean *in vitro* blood-to-plasma ratio of 1.35. *In vitro* studies suggest that ceritinib is a substrate for P-glycoprotein (P-gp), but not of breast cancer resistance protein (BCRP) or multi-resistance protein 2 (MRP2). The *in vitro* apparent passive permeability of ceritinib was determined to be low.

In rats, ceritinib crosses the intact blood brain barrier with a brain-to-blood exposure (AUC_{inf}) ratio of about 15%. There are no data related to brain-to-blood exposure ratio in humans.

Biotransformation

In vitro studies demonstrated that CYP3A was the major enzyme involved in the metabolic clearance of ceritinib.

Following a single oral administration of radioactive ceritinib dose at 750 mg, ceritinib was the main circulating component in human plasma. A total of 11 metabolites were found circulating in plasma at low levels with mean contribution to the radioactivity AUC of ≤2.3% for each metabolite. Main biotransformation pathways identified in healthy subjects included mono-oxygenation, O-dealkylation, and N-formylation. Secondary biotransformation pathways involving the primary biotransformation products included glucuronidation and dehydrogenation. Addition of a thiol group to O-dealkylated ceritinib was also observed.

Elimination

Following single oral doses of ceritinib, the geometric mean apparent plasma terminal half-life ($T_{½}$) of ceritinib ranged from 31 to 41 hours in patients over the 400 to 750 mg dose range. Daily oral dosing of ceritinib results in achievement of steady-state by approximately 15 days and remains stable afterwards, with a geometric mean accumulation ratio of 6.2 after 3 weeks of daily dosing. The geometric mean apparent clearance (CL/F) of ceritinib was lower at steady-state (33.2 litres/hour) after 750 mg daily oral dosing than after a single 750 mg oral dose (88.5 litres/hour), suggesting that ceritinib demonstrates non-linear pharmacokinetics over time.

The primary route of excretion of ceritinib and its metabolites is in the faeces. Recovery of unchanged ceritinib in the faeces accounts for a mean 68% of an oral dose. Only 1.3% of the administered oral dose is recovered in the urine.

Special populations

Hepatic impairment
A dedicated pharmacokinetic study in patients with hepatic impairment has not been conducted. Based on available data, ceritinib is eliminated primarily via the liver. Therefore, hepatic impairment may increase ceritinib plasma concentrations.

Based on a population pharmacokinetic analysis of 48 patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin >1.0 to 1.5 times ULN and any AST) and 254 patients with normal hepatic function (total bilirubin ≤ULN and AST ≤ULN), ceritinib exposures were similar in patients with mild hepatic impairment and normal hepatic function. Dose adjustment is not recommended for patients with mild hepatic impairment based on the results of a population pharmacokinetic analysis. The pharmacokinetics of ceritinib have not been studied in patients with moderate to severe hepatic impairment. Ceritinib is not recommended in these patients (see section 4.2).

Renal impairment
A dedicated pharmacokinetic study in patients with renal impairment has not been conducted. Based on available data, ceritinib elimination via the kidney is negligible (1.3% of a single oral administered dose).

Based on a population pharmacokinetic analysis of 97 patients with mild renal impairment (CLcr 60 to <90 ml/min), 22 patients with moderate renal impairment (CLcr 30 to <60 ml/min) and 183 patients with normal renal function (≥90 ml/min), ceritinib exposures were similar in patients with mild and moderate renal impairment and normal renal function, suggesting that no dose adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment (CLcr <30 ml/min) were not included in the clinical studies of Zykadia (see section 4.2).

Effects of age, gender, and race
Population pharmacokinetic analyses showed that age, gender and race had no clinically meaningful influence on ceritinib exposure.

Cardiac electrophysiology
The potential for QT interval prolongation of ceritinib was assessed in four clinical studies with Zykadia. Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of ceritinib on the QT interval. A central analysis of ECG data demonstrated new QTc >500 msec in one patient (0.2%). There were 23 patients (4.4%) with a QTc increase from baseline >60 msec. A concentration-QTc response analysis based on the data from Study A demonstrated that at average steady-state concentrations the upper bound of the 2-sided 90% CI for QTc increase from baseline was 16 msec at Zykadia 750 mg. A pharmacokinetic analysis suggested that ceritinib causes concentration-dependent increases in QTc (see section 4.4).

5.3 Preclinical safety data

Safety pharmacology studies indicate that ceritinib is unlikely to interfere with vital functions of the respiratory and central nervous systems. *In vitro* data show that the IC50 for the inhibitory effect of ceritinib on the hERG potassium channel was 0.4 micromolar. An *in vivo* telemetry study in monkeys showed a modest QT prolongation in 1 of 4 animals after receiving the highest dose of ceritinib. ECG studies in monkeys after 4- or 13-weeks of dosing with ceritinib have not shown QT prolongation or abnormal ECGs.

The micronucleus test in TK6 cells was positive. No signs of mutagenicity or clastogenicity were observed in other *in vitro* and *in vivo* genotoxicity studies with ceritinib. Therefore, genotoxic risk is not expected in humans.

Carcinogenicity studies have not been performed with ceritinib.

Reproductive toxicology studies (i.e. embryo-foetal development studies) in pregnant rats and rabbits indicated no foetotoxicity or teratogenicity after dosing with ceritinib during organogenesis; however, maternal plasma exposure was less than that observed at the recommended dose of 750 mg in clinical trials. Formal non-clinical studies on the potential effects of ceritinib on fertility have not been conducted.

The principal toxicity related to ceritinib administration in rats and monkeys was inflammation of the extra-hepatic bile ducts accompanied by increased neutrophil counts in the peripheral blood. Mixed cell/neutrophilic inflammation of the extra-hepatic ducts extended to the pancreas and/or duodenum at higher doses. Gastrointestinal toxicity was observed in both species characterised by body weight loss, decreased food consumption, emesis (monkey), diarrhoea and, at high doses, by histopathological lesions including erosion, mucosal inflammation and foamy macrophages in the duodenal crypts and submucosa. The liver was also affected in both species, at exposures that approximate clinical exposures at the recommended dose of 750 mg, and included minimal increases in liver transaminases in a few animals and vacuolation of the intra-hepatic bile duct epithelium. Alveolar foamy macrophages (confirmed phospholipidosis) were seen in the lungs of rats, but not in monkeys, and the lymph nodes of rats and monkeys had macrophage aggregates. Target organ effects showed partial to complete recovery.

Effects on the thyroid were observed in both rat (mild increases in thyroid stimulating hormone 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 thyroid stimulating hormone 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Microcrystalline cellulose
Low substituted-hydroxypropylcellulose
Sodium starch glycolate (type A)
Magnesium stearate
Silica, colloidal anhydrous

Capsule shell

Gelatin
Indigotine (E132)
Titanium dioxide (E171)

Printing ink

Shellac (bleached, de-waxed) glaze 45%
Iron oxide black (E172)
Propylene glycol
Ammonium hydroxide 28%

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/polychlorotrifluoroethylene (PCTFE) – Alu blisters containing 10 hard capsules.

Multipacks containing 150 (3 packs of 50) hard capsules and unit packs containing 40 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/999/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 May 2015
Date of latest renewal: 22 March 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm the efficacy of ceritinib in the treatment of patients previously treated with crizotinib, the MAH should submit the final results of the phase III efficacy study A2303 comparing ceritinib to chemotherapy.	30 September 2018

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Zykadia 150 mg hard capsules
Ceritinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 150 mg ceritinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

40 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/999/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zykadia 150 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Zykadia 150 mg hard capsules
Ceritinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 150 mg ceritinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

Multipack: 150 (3 packs of 50) hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/999/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zykadia 150 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Zykadia 150 mg hard capsules
Ceritinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains 150 mg ceritinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

50 hard capsules. Component of a multipack. Cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/999/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Zykadia 150 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Zykadia 150 mg hard capsules
Ceritinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Zykadia 150 mg hard capsules
Ceritinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zykadia is and what it is used for

What Zykadia is
Zykadia is a cancer medicine that contains the active substance ceritinib. It is used to treat adults with advanced stages of a form of lung cancer called non-small cell lung cancer (NSCLC). Zykadia is only given to patients whose disease is due to a defect in a gene called ALK (anaplastic lymphoma kinase).

How Zykadia works
In patients with ALK defects, an abnormal protein is produced that stimulates the growth of the cancer cells. Zykadia blocks the action of this abnormal protein and thus slows down the growth and spread of NSCLC.

If you have any questions about how Zykadia works or why this medicine has been prescribed for you, ask your doctor or pharmacist.

2. What you need to know before you take Zykadia

Do not take Zykadia:
– if you are allergic to ceritinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Zykadia:
- if you have problems with your liver.
- if you have problems with your lungs or problems breathing.
- if you have problems with your heart, including reduced heart rate, or if the results of an electrocardiogram (ECG) have shown that you have an abnormality of the electrical activity of your heart known as "prolonged QT interval".
- if you have diabetes (high level of sugar in your blood).
- if you have problems with your pancreas.
- if you are currently taking steroids.

Tell your doctor or pharmacist immediately if you get any of the following signs or symptoms during treatment with Zykadia:
- tiredness, itchy skin, yellowing of your skin or the whites of your eyes, nausea (feeling sick) or vomiting, decreased appetite, pain on the right side of your abdomen (belly), dark or brown urine, bleeding or bruising more easily than normal. These may be signs or symptoms of liver problems.
- new or worsening cough with or without mucus, fever, chest pain, trouble breathing or shortness of breath. These may be symptoms of lung problems.
- chest pain or discomfort, changes in your heartbeat (fast or slow), light-headedness, fainting, dizziness, blue discoloration of your lips, shortness of breath, swelling of your lower limbs or skin. These may be signs or symptoms of heart problems.
- severe diarrhoea, nausea or vomiting. These are symptoms of digestive problems.
- excessive thirst or increased frequency of urination. These may be symptoms of a high level of sugar in the blood.

Your doctor may need to adjust your treatment or stop Zykadia temporarily or permanently.

Blood tests during treatment with Zykadia
Your doctor should perform blood tests before you start treatment, every 2 weeks for the first month of treatment and every month during treatment. The purpose of these tests is to check your liver function. Your doctor should also perform blood tests to check the functioning of your pancreas and the level of sugar in your blood before you start treatment with Zykadia and regularly during treatment.

Children and adolescents
The use of Zykadia in children and adolescents up to 18 years of age is not recommended.

Other medicines and Zykadia
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription such as vitamins or herbal supplements, because they might interact with Zykadia. It is particularly important that you mention any of the following medicines.

Medicines which may increase the risk of side effects with Zykadia:
- medicines used to treat AIDS/HIV (e.g. ritonavir, saquinavir).
- medicines used to treat infections. These include medicines that treat fungal infections (antifungals such as ketoconazole, itraconazole, voriconazole, posaconazole) and medicines that treat certain types of bacterial infection (antibiotics such as telithromycin).

The following medicines may reduce the effectiveness of Zykadia:
- St. John's Wort, a herbal medicine used to treat depression.
- medicines used to stop seizures or fits (anti-epileptics such as phenytoin, carbamazepine, or phenobarbital).
- medicines used to treat tuberculosis (e.g. rifampicin, rifabutin).

Zykadia may increase the side effects associated with the following medicines:
- medicines used to treat irregular heartbeat or other heart problems (e.g. amiodarone, disopyramide, procainamide, quinidine, sotalol, dofetilide, ibutilide and digoxin).
- medicines used to treat stomach problems (e.g. cisapride).
- medicines used to treat mental health problems (e.g. haloperidol, droperidol, pimozide).
- medicines used to treat depression (e.g. nefazodone).
- midazolam, a medicine used to treat acute seizures or as a sedative before or during surgery or medical procedures.
- warfarin and dabigatran, medicines used to prevent blood clots.
- diclofenac, a medicine used to treat joint pain and inflammation.
- alfentanil and fentanyl, medicines used to treat severe pain.
- astemizole, an antihistamine medicine used to prevent allergies.
- ciclosporin, sirolimus and tacrolimus, medicines used in organ transplantation to prevent transplant organ rejection.
- ergotamine, a medicine used to treat migraine.
- domperidone, a medicine used to treat nausea and vomiting.
- moxifloxacin and clarithromycin, medicines used to treat bacterial infections.
- methadone, a medicine used to treat pain and for the treatment of opioid dependence.
- chloroquine and halofantrine, medicines used to treat malaria.
- topotecan, a medicine used to treat certain types of cancer.
- colchicine, a medicine used to treat gout.
- pravastatine and rosuvastatine, medicines used to reduce cholesterol levels.
- sulfasalazine, a medicine used to treat inflammatory bowel disease or rheumatoid arthritis.

Ask your doctor or pharmacist if you are not sure whether your medicine is one of the medicines listed above.

These medicines should be used with care or may need to be avoided during your treatment with Zykadia. If you are taking any of these, your doctor might need to prescribe an alternative medicine for you.

You should also tell your doctor if you are already taking Zykadia and you are prescribed a new medicine that you have not already taken at the same time as Zykadia.

Oral contraceptives
If you take Zykadia whilst using oral contraceptives, the oral contraceptives may become ineffective.

Zykadia with food and drink
You should not eat grapefruit or drink grapefruit juice during treatment. It may make the amount of Zykadia in your blood increase to a harmful level.

Pregnancy and breast-feeding
You must use a highly effective method of birth control during treatment with Zykadia and for 3 months after stopping treatment. Talk to your doctor about the birth control methods that may be right for you.

Zykadia is not recommended during pregnancy unless the potential benefit outweighs the potential risk to the baby. If you are pregnant, think you might be pregnant or plan to become pregnant, ask your doctor for advice. Your doctor will discuss with you the potential risks of taking Zykadia during pregnancy.

Zykadia should not be used during breast-feeding. You and your doctor will decide together whether you should breast-feed or take Zykadia. You should not do both.

Driving and using machines
You should take special care when driving and using machines when taking Zykadia as you may experience visual disturbances or tiredness.

3. How to take Zykadia

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

How much to take
The recommended dose is 750 mg (five capsules) once daily. Your doctor will tell you exactly how many capsules you need to take. Do not change the dose without talking to your doctor.
- Take Zykadia once a day at about the same time each day.
- Take the capsules on an empty stomach. Do not eat any food for at least two hours before taking the dose and at least two hours after taking it.
- Swallow the capsules whole with water. Do not chew or crush them.
- If you have to vomit after you swallow the Zykadia capsules, do not take any more capsules until your next scheduled dose.

How long to take Zykadia
- Continue taking Zykadia for as long as your doctor tells you.
- This is a long-term treatment, possibly lasting for months. Your doctor will monitor your condition to see that the treatment is having the desired effect.

If you have questions about how long to take Zykadia, talk to your doctor or pharmacist.

If you take more Zykadia than you should
If you accidentally take too many capsules, or if someone else accidentally takes your medicine, contact a doctor or hospital for advice immediately. Medical treatment may be necessary.

If you forget to take Zykadia
What to do if you forget to take a dose depends on how long it is until your next dose.
- If your next dose is in 12 hours or more, take the missed capsules as soon as you remember. Then take the next capsules at the usual time.
- If your next dose is in less than 12 hours, skip the missed capsules. Then take the next capsules at the usual time.

Do not take a double dose to make up for a forgotten dose.

If you stop taking Zykadia
Do not stop taking this medicine before talking to your doctor. If you have any questions contact your doctor right away.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

STOP taking Zykadia and seek medical help immediately if you experience any of the following, which may be signs of an allergic reaction:
- Difficulty in breathing or swallowing
- Swelling of the face, lips, tongue or throat
- Severe itching of the skin, with a red rash or raised bumps

Some side effects could be serious
If you experience any of the following side effects, tell your doctor or pharmacist immediately:
- Chest pain or discomfort, changes in your heartbeat (fast or slow), light-headedness, fainting, dizziness, blue discoloration of your lips, shortness of breath, swelling of your lower limbs or skin (potential signs or symptoms of heart problems)
- New or worsening cough with or without mucus, fever, chest pain, trouble breathing or shortness of breath (potential signs of lung problems)
- Tiredness, itchy skin, yellowing of your skin or the whites of your eyes, nausea (feeling sick) or vomiting, decreased appetite, pain on the right side of your abdomen (belly), dark or brown urine, bleeding or bruising more easily than normal (potential signs or symptoms of liver problems)
- Severe diarrhoea, nausea or vomiting
- Excessive thirst, increased frequency of urination (symptoms of high level of glucose in the blood)
- Severe upper stomach pain (sign of inflammation of the pancreas, also known as pancreatitis)

Other possible side effects
Other side effects are listed below. If these side effects become severe, please tell your doctor or pharmacist.

Very common (may affect more than 1 in 10 people):
- Tiredness (fatigue)
- Abnormal results of blood tests to check liver function (high levels of enzymes called alanine aminotransferase and/or aspartate aminotransferase and/or gamma glutamyltransferase, high levels of bilirubin)
- Abdominal pain
- Decreased appetite
- Constipation
- Rash
- Abnormal results of blood tests to check kidney function (high level of creatinine)
- Heartburn (potential sign of a disorder of the digestive tract)
- Reduction in the number of red blood cells, known as anaemia

Common (may affect up to 1 in 10 people):
- Vision problems
- Low level of phosphate in the blood (this would be detected during blood tests)
- High level of enzymes called lipase and/or amylase in the blood (this would be detected during blood tests)
- Significantly decreased urine flow (potential sign of a kidney problem)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zykadia

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.
- This medicine does not require any special storage conditions.
- Do not use this medicine if you notice any damage to the packaging or if there are any signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zykadia contains
- The active substance of Zykadia is ceritinib. Each hard capsule contains 150 mg of ceritinib.
- The other ingredients are:
  - Capsule contents: silica, colloidal anhydrous, low substituted-hydroxypropylcellulose, sodium starch glycolate (type A), magnesium stearate and microcrystalline cellulose.
  - Capsule shell: gelatin, indigotine (E132) and titanium dioxide (E171).
  - Printing ink: Shellac (bleached, de-waxed) glaze 45%, iron oxide black (E172), propylene glycol and ammonium hydroxide 28%.

What Zykadia looks like and contents of the pack
Zykadia hard capsules have a white opaque body and blue opaque cap, with "LDK 150MG" imprinted on the cap and "NVR" on the body. They contain white to almost white powder.

The capsules are provided in blisters and are available in packs containing 40 capsules or in multipacks containing 150 capsules (3 packs of 50). Not all pack sizes may be marketed in your country.

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This leaflet was last revised in

This medicine has been given "conditional approval". This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu