For the use of only Registered Medical Practitioners or a Hospital or a Laboratory.

ZYKADIA ™

Ceritinib 150 mg hard gelatin capsules

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Hard gelatin capsules

150 mg: Size #00 opaque white and opaque blue capsule, opaque blue cap marked in black ink with "LDK 150MG", opaque white body marked in black ink with "NVR", containing white to almost white powder.

Active substance

Ceritinib

Each capsule contains 150 mg ceritinib free base.

Active moiety

Ceritinib

Excipients

Capsule content: colloidal anhydrous silica; L-hydroxypropylcellulose; magnesium stearate; microcrystalline cellulose; sodium starch glycolate

Capsule shell: gelatin; indiogotine (E132); titanium dioxide (E171)

Pharmaceutical formulations may vary between countries.

INDICATIONS

Zykadia is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive.

DOSAGE AND ADMINISTRATION

General Target Population

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.

Continue treatment as long as the patient is deriving clinical benefit from therapy.

Dose modifications

Temporary dose interruption and/or dose reduction of Zykadia therapy may be required based on individual safety and tolerability. If dose reduction is required due to any adverse drug reaction, then the dose of Zykadia should be reduced by decrements of 150 mg daily. Early identification and management of adverse drug reactions (including gastrointestinal disorders) with standard supportive care measures should be considered.

Table 1 summarizes recommendations for dose interruption, reduction, or discontinuation of Zykadia in the management of select adverse drug reactions (ADRs).

Table 1 - Zykadia dose adjustment and management recommendations for adverse drug reactions

Criteria	Zykadia Dosing
Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation greater than 5 times upper limit of normal (ULN) with total bilirubin less than or equal to 1.5 times ULN	Withhold Zykadia until recovery to baseline or less than or equal to 3 times ULN, then reinitiate Zykadia by reducing dose by one decrement
ALT or AST elevation greater than 3 times ULN with concurrent total bilirubin elevation greater than 1.5 times ULN (in the absence of cholestasis or hemolysis)	Permanently discontinue Zykadia
Any Grade treatment-related pneumonitis	Permanently discontinue Zykadia
QTc greater than 500 msec on at least 2 separate electrocardiograms (ECGs)	Withhold Zykadia until recovery to baseline or to a QTc less than 481 msec, then reinitiate Zykadia by reducing dose by one decrement
QTc greater than 500 msec or greater than 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 bradycardia or to a heart rate of 60 bpm or above Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications If contributing concomitant medication is identified and discontinued, or its dose is adjusted, reinitiate Zykadia at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, reinitiate Zykadia by reducing dose 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 medication is identified If contributing concomitant medication is identified and discontinued, or its dose is adjusted, reinitiate Zykadia by reducing dose by two decrements upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring[b]

[a] Heart rate less than 60 beats per minutes (bpm)
[b] Permanently discontinue for recurrence

Special populations

Patients with renal impairment

Ceritinib has not been studied in patients with renal impairment. However, based upon 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 Zykadia in this population (see section CLINICAL PHARMACOLOGY).

Patients with hepatic impairment

Ceritinib has not been studied in patients with hepatic impairment. Based upon available data, ceritinib is eliminated primarily via the liver. Therefore, caution should be used in patients with hepatic impairment (see section CLINICAL PHARMACOLOGY).

Pediatric patients

The safety and efficacy of Zykadia have not been established in pediatric patients.

Geriatric patients (≥65 years)

The limited data on the safety and efficacy of Zykadia in patients aged 65 years and older do not suggest that a dose adjustment is required in elderly patients (see section CLINICAL PHARMACOLOGY).

Method of administration

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

If a dose is missed, the patient should not take the missed dose, but take the next prescribed dose.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Hepatotoxicity

ALT and AST elevations have been observed in patients treated with Zykadia. The majority of cases were manageable with dose interruption and/or dose reduction. Few events required discontinuation of Zykadia. Cases of drug-induced liver injury occurred in less than 1% of patients. There were no fatal cases.

Monitor with liver laboratory tests (including ALT, AST, and total bilirubin) prior to the start of treatment and monthly thereafter. In patients who develop transaminase elevations, more frequent monitoring of liver transaminases and total bilirubin should be done as clinically indicated (see section DOSAGE AND ADMINISTRATION and section ADVERSE DRUG REACTIONS).

Pneumonitis

Severe, life-threatening, or fatal pneumonitis has been observed in patients treated with Zykadia. Most cases improved or resolved with interruption of Zykadia.

Monitor patients for pulmonary symptoms indicative of pneumonitis. Exclude other potential causes of pneumonitis, and permanently discontinue Zykadia in patients diagnosed with treatment-related pneumonitis (see section DOSAGE AND ADMINISTRATION and section ADVERSE DRUG REACTIONS).

QT interval prolongation

QTc prolongation has been observed. A central analysis of ECG data demonstrated new QTc >500 msec in 1 patient (0.3%). There were 7 patients (2.3%) with a QTc increase from baseline >60 msec. A pharmacokinetic analysis suggested that ceritinib causes concentration-dependent increases in QTc. There have been no cases of Torsade de pointes and no fatal cases.

Avoid use of Zykadia in patients with congenital long QT syndrome. Consider periodic monitoring with ECGs and periodic monitoring of electrolytes in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QT interval. Permanently discontinue Zykadia in patients who develop QTc greater than 500 msec or greater than 60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. Withhold Zykadia in patients who develop QTc greater than 500 msec on at least 2 separate ECGs until recovery to baseline or a QTc less than 481 msec, then reinitiate Zykadia by reducing dose by one decrement (see section DOSAGE AND ADMINISTRATION, section ADVERSE DRUG REACTIONS and section CLINICAL PHARMACOLOGY).

Bradycardia

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If a dose is missed, the patient should not take the missed dose, but take the next prescribed dose.

CONTRAINDICATIONS

None.

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Bradycardia

Asymptomatic cases of bradycardia have been observed in patients treated with Zykadia. Avoid use of Zykadia in combination with other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible. Monitor heart rate and blood pressure regularly. In cases of symptomatic bradycardia that is not life-threatening, withhold Zykadia until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, evaluate the use of concomitant medications, and adjust the dose of Zykadia if necessary. Permanently discontinue Zykadia for life-threatening bradycardia if no contributing concomitant medication is identified; however, if associated with concomitant medication known to cause bradycardia or hypotension, withhold Zykadia until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, and if concomitant medication can be adjusted or discontinued, reinitiate Zykadia by reducing dose by two decrements upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring (see section DOSAGE AND ADMINISTRATION and section ADVERSE DRUG REACTIONS).

ADVERSE DRUG REACTIONS

Summary of the safety profile

The data described below are based on an open-label, dose-escalation and expansion study investigating the safety, pharmacokinetics, and anti-tumor activity of Zykadia in patients with tumors confirmed to have genetic abnormalities in ALK. Adverse drug reaction (ADR) information is based on safety data from this registration study in 255 patients (246 ALK-positive NSCLC patients and 9 non-NSCLC patients) treated at the recommended dose of 750 mg of Zykadia.

The median exposure to Zykadia was 19.6 weeks (range: 0.4 to 71.4 weeks). The median relative dose intensity was 87.3% (range: 41.5% to 100%); the median dose intensity was 654.5 mg/day (range: 311 mg/day to 750 mg/day). Dosing interruptions occurred in 60.8% of patients. Dose reductions occurred in 52.2% of patients. The rate of adverse events resulting in permanent discontinuation was 9.4%.

ADRs with an incidence of ≥10% were diarrhea, nausea, vomiting, abdominal pain, fatigue, ALT increased, decreased appetite, AST increased, constipation, esophageal disorder, blood creatinine increased, and rash.

Grade 3-4 ADRs with an incidence of ≥5% were ALT increased, AST increased, diarrhea, lipase increased, and hyperglycemia. Pneumonia was the only serious adverse event reported in ≥5% of patients.

Dose reduction or interruption for adverse events of diarrhea, nausea, and vomiting was needed in 13.7%, 15.3%, and 13.3% of patients, respectively. No patients discontinued Zykadia due to an adverse event of diarrhea; adverse events of nausea and vomiting resulted in Zykadia discontinuation in 0.4% of patients each.

Among the 255 patients, deaths within 28 days of the last dose of Zykadia occurred in 28 patients. Causes of death included study indication (18 patients) and "other" causes (10). "Other" causes of death included pneumonia (2), respiratory failure, interstitial lung disease, aspiration pneumonia, pneumothorax, gastric hemorrhage, general physical health deterioration, pulmonary tuberculosis, and sepsis (1 each).

Tabulated summary of adverse drug reactions from clinical trials

Table 2 presents the frequency category of ADRs reported for Zykadia in the registration study.

ADRs are listed according to MedDRA system organ class. Within each system organ class, the adverse drug reactions 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 adverse drug reaction: 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 - Adverse drug reactions in patients treated at a dose of 750 mg

Primary System Organ Class Preferred Term	Zykadia N=255 n (%)	Frequency category
Blood and lymphatic system disorders		
Anemia	22 (8.6)	Common
Metabolism and nutrition disorders		
Decreased appetite	79 (31.0)	Very common
Hyperglycemia	16 (6.3)	Common
Hypophosphatemia	14 (5.5)	Common
Eye disorders		
Vision disorder[a]	21 (8.2)	Common
Cardiac disorders		
Bradycardia[b]	8 (3.1)	Common
Respiratory, thoracic and mediastinal disorders		
Pneumonitis*[c]	9 (3.5)	Common
Gastrointestinal disorders		
Diarrhea	214 (83.9)	Very common
Nausea	196 (76.9)	Very common
Vomiting	144 (56.5)	Very common
Abdominal pain[d]	124 (48.6)	Very common
Constipation	65 (25.5)	Very common
Esophageal disorder[e]	39 (15.3)	Very common
Hepatobiliary disorders		
Drug-induced liver injury**	1 (0.4)	Uncommon
Skin and subcutaneous tissue disorders		
Rash[f]	33 (12.9)	Very common

Primary System Organ Class Preferred Term	Zykadia N=255 n (%)	Frequency category
Renal and urinary disorders		
Renal failure[g]	6 (2.4)	Common
Renal impairment[h]	4 (1.6)	Common
General disorders and administration site conditions		
Fatigue[i]	120 (47.1)	Very common
Investigations		
Alanine aminotransferase increased	91 (35.7)	Very common
Aspartate aminotransferase increased	67 (26.3)	Very common
Blood creatinine increased	34 (13.3)	Very common
Lipase increased	18 (7.1)	Common
Electrocardiogram QT prolonged	9 (3.5)	Common
Blood bilirubin increased	6 (2.4)	Common

* An SAE of pneumonitis is not included in the table above as it was not reported in the clinical database at the time of the database lock for the study.
** An additional case was reported in a Japanese phase I dose-escalation and expansion study and is not included in the table above.
Includes cases reported within the clustered terms:
[a] Vision disorder (vision impairment, vision blurred, photopsia, vitreous floaters, accommodation disorder, presbyopia, visual acuity reduced)
[b] Bradycardia (bradycardia, sinus bradycardia)
[c] Pneumonitis (interstitial lung disease, pneumonitis)
[d] Abdominal pain (abdominal pain, abdominal pain upper, abdominal discomfort, epigastric discomfort)
[e] Esophageal disorder (dyspepsia, gastroesophageal reflux disease, dysphagia)
[f] Rash (rash, dermatitis acneiform)
[g] Renal failure (renal failure acute, renal failure)
[h] Renal impairment (azotemia, renal impairment)
[i] Fatigue (fatigue, asthenia)

Special populations

In the registration study, 40 patients (15.7%) treated with Zykadia were aged 65 years and older. The safety profile in patients aged 65 years and older was similar to that in patients less than 65 years of age (see section DOSAGE AND ADMINISTRATION).

INTERACTIONS

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 AUCinf and Cmax, respectively, compared to when ceritinib was given alone. Co-administration of ceritinib with strong CYP3A/P-gp inhibitors increases ceritinib plasma concentrations. Avoid concomitant use of strong CYP3A inhibitors, including but not limited to, ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, and nefazodone. Exercise caution with concomitant use of moderate CYP3A inhibitors and carefully monitor adverse drug reactions.

Based on *in vitro* data, ceritinib is a substrate of the efflux transporter P-glycoprotein (P-gp). If ceritinib is administered with drugs that inhibit P-gp, an increase in ceritinib concentration is likely. Exercise caution with concomitant use of P-gp inhibitors and carefully monitor adverse drug reactions.

Agents that may decrease ceritinib plasma concentrations

In healthy subjects, co-administration of a single 750 mg ceritinib dose with rifampin (600 mg daily for 14 days), a strong CYP3A/P-gp inducer, resulted in 70% and 44% decreases in ceritinib AUCinf and Cmax, respectively, compared to when ceritinib was given alone. Co-administration of ceritinib with strong CYP3A/P-gp inducers decreases ceritinib plasma concentrations. Avoid concomitant use of strong CYP3A inducers, including but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort *(Hypericum perforatum)*. Exercise caution with concomitant use of P-gp inducers.

Agents whose plasma concentration may be altered by ceritinib

Based on *in vitro* data, ceritinib competitively inhibited the metabolism of a CYP3A substrate, midazolam, and a CYP2C9 substrate, diclofenac. Time-dependent inhibition of CYP3A was also observed. The steady-state Cmax 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 metabolized by these enzymes at clinically relevant concentrations. Dose reduction may be needed for co-administered medicines that are predominantly metabolized by CYP3A and CYP2C9. Avoid co-administration of ceritinib with CYP3A substrates known to have narrow therapeutic indices (e.g., cisapride, pimozide, and quinidine) and CYP2C9 substrates known to have narrow therapeutic indices (e.g., phenytoin and warfarin) .

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 drugs that are predominantly metabolized by these enzymes. Exercise caution with concomitant use of CYP2A6 and CYP2E1 substrates and carefully monitor adverse drug reactions.

Agents that are substrates of transporters

Based on *in vitro* data, ceritinib did not inhibit apical efflux transporters, BCRP, P-gp or 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.

Drug-food/drink interactions

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

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

WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY

Women of child-bearing potential (and contraceptive measures if applicable)

Women of childbearing potential should be advised to use a highly effective method of contraception while receiving Zykadia and for up to 3 months after discontinuing treatment.

Pregnancy

There are no data regarding the use of Zykadia in pregnant women. Reproductive toxicology studies (i.e., embryo-fetal development 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 recommended dose of 750 mg in clinical trials. The potential risk in humans is unknown. Zykadia should not be given to pregnant women unless the potential benefit outweighs the potential risk to the fetus.

Breast-feeding

It is unknown 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 breastfed newborns/infants, a decision should be made whether to abstain from breast-feeding or abstain from using Zykadia taking into account the importance of Zykadia to the mother.

Fertility

The potential for Zykadia to cause infertility in male and female patients is unknown.

OVERDOSAGE

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

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

Ceritinib is an orally highly selective and potent ALK kinase inhibitor. Ceritinib inhibits autophosphorylation of ALK, ALK-mediated phosphorylation of downstream signaling 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 effective against EML4-ALK kinase activity in a NSCLC cell line (H2228), resulting in inhibition of cell proliferation *in vitro* and regression of tumors in H2228 derived xenografts in mouse and rat.

Pharmacodynamics (PD)

Ceritinib inhibition of ALK kinase activity and ALK-mediated signaling pathways in Karpas 299 (lymphoma cell line) and in H2228 (lung cancer cell line) was demonstrated to be dose-dependent. The inhibitory effect of ceritinib led to inhibition of cancer cell proliferation *in vitro* and tumor regression *in vivo* in mouse and rat xenograft models. Ceritinib is approximately 20-fold more potent than crizotinib in enzymatic inhibition assays of the ALK kinase activity (IC50 for inhibition of ALK of 0.15 nanomolar for ceritinib and 3 nanomolar for crizotinib). In a kinase panel of 36 enzymes, ceritinib inhibited only 2 other kinases with approximately 50-fold less potency for ALK inhibition. All other kinases in the panel had greater than 500-fold less potency when compared with ALK, demonstrating a high degree of selectivity. A single-dose pharmacodynamic study and multiple-daily dose efficacy study performed in Karpas299 lymphoma and H2228 lung cancer tumor models indicated that a 60% to 80% reduction in the ALK signaling pathway may be required to achieve tumor regression.

Pharmacokinetics (PK)

Absorption

Peak plasma levels (Cmax) 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 feces. The absolute bioavailability of ceritinib has not been determined.

Systemic exposure to ceritinib is increased when administered with food. Ceritinib AUCinf values were approximately 58% and 73% higher (Cmax 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 Cmax and AUClast, increased dose-proportionally over the 50 to 750 mg dose range. In contrast with single-dose data, pre-dose concentration (Cmin) 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 (AUCinf) ratio of about 15%. There are no data related to brain-to-blood exposure ratio in humans.

Biotransformation/metabolism

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 (T1/2) 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 L/hr) after 750 mg daily oral dosing than after a single 750 mg oral dose (88.5 L/hr) suggesting that ceritinib demonstrates non-linear PK over time.

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

Special populations

Patients with hepatic impairment

Ceritinib has not been studied in patients with hepatic impairment. However, based upon available data, ceritinib is eliminated primarily via the liver. Therefore, hepatic impairment is likely to increase ceritinib plasma concentrations.

A population pharmacokinetic analysis indicates that no significant influence of baseline ALT and total bilirubin was detected on the apparent clearance (CL/F) of ceritinib. However, the analysis is limited by the fact that there are no data available for patients with moderate or severe hepatic impairment

Patients with renal impairment

Ceritinib has not been studied in patients with renal impairment. However, based upon available data, ceritinib elimination via the kidney is negligible (1.3% of a single oral administered dose).

A population pharmacokinetic analysis indicates that no significant influence of baseline estimated glomerular filtration rate (>30 mL/min/1.73 m^2) was detected on the apparent clearance (CL/F) of ceritinib suggesting that no dose adjustment is necessary in patients with mild to moderate renal impairment. There are no data available for patients with severe renal impairment.

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 an open-label, dose-escalation and expansion study investigating the safety, pharmacokinetics, and anti-tumor activity of ceritinib in patients with tumors confirmed to have genetic abnormalities in ALK. Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of ceritinib on the QT interval. In the registration study, a central analysis of ECG data demonstrated new QTc >500 msec in 1 patient (0.3%). There were 7 patients (2.3%) with a QTc increase from baseline >60 msec. A pharmacokinetic analysis suggested that ceritinib causes concentration-dependent increases in QTc (see section WARNINGS AND PRECAUTIONS).

CLINICAL STUDIES

The use of Zykadia in the treatment of ALK-positive NSCLC was investigated in a multicenter, open-label study which included a dose-escalation phase and an expansion phase at the recommended dose of 750 mg. All patients enrolled in the registration study had locally advanced or metastatic malignancy that had progressed despite standard therapy and all patients were previously tested for ALK rearrangement. Patients with controlled or asymptomatic brain metastases were eligible for the study. Prior ALK inhibitor therapy was permitted. Two-hundred and ninety of the 304 patients enrolled in the study were ALK-positive NSCLC patients. At the time of the data cut-off, 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.

The primary evaluation was based on overall response rate (ORR) and duration of response (DOR) by Investigator assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 for patients who had received the first dose of Zykadia at least 18 weeks prior to the data cut-off, and who were treated with a Zykadia dose of 750 mg. Additional evaluations included progression-free survival (PFS) by Investigator assessment.

Across the 246 ALK-positive NSCLC patients treated at a dose of 750 mg in the registration study, the median age was 53 years (range: 22-80 years); 84.1% of patients were younger than 65 years. A total of 53.7% of patients were female. Caucasians comprised 63.4% of the study population, Asians 33.3%, Blacks 1.6%, and other races 1.6%. The vast majority of patients had adenocarcinoma (92.7%) and were either never or former smokers (97.6%). More than two-thirds (67.5%) of the patients were treated with 2 or more regimens prior to enrollment into the study, 26.0% with 1 prior regimen, and 6.5% with 0 prior regimens.

Of the 246 ALK-positive NSCLC patients treated at a dose of 750 mg, there were 180 response-evaluable patients who had received the first dose of Zykadia at least 18 weeks prior to the data cut-off and were treated with a Zykadia dose of 750 mg. Of these 180 patients, 108 (60.0%; 95% CI: 52.4, 67.2) patients had a tumor response that was confirmed at least 4 weeks after the initial assessment (Table 3). The median time to the first objective tumor response (complete response [CR] or partial response [PR]) that was subsequently confirmed was 6.1 weeks. The median DOR in patients who responded was 9.69 months (95% CI: 6.93, 11.40). The median PFS was 6.97 months (95% CI: 6.21, 10.12). Patients responded to Zykadia regardless of whether they received a prior ALK inhibitor. In patients who had previously received treatment with an ALK inhibitor, the response rate was 55.4% (95% CI: 46.1, 64.4), and in patients who were ALK inhibitor naïve, it was 69.5% (95% CI: 56.1, 80.8).

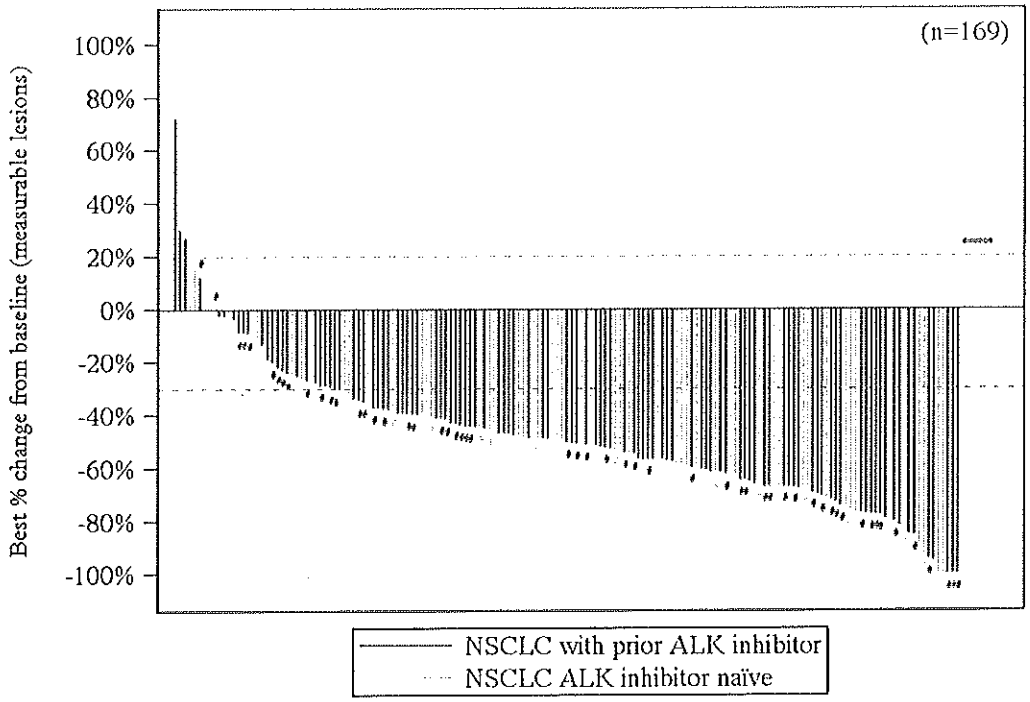
Table 3 - Locally advanced or metastatic ALK-positive NSCLC efficacy results for the 750 mg treatment dose group[a]

Efficacy Parameter	All Patients (N=180)	Prior ALK inhibitor (N=121)	ALK inhibitor naïve (N=59)
Overall Response Rate (CR+PR)[b] [% (95% CI)]	60.0% (52.4, 67.2)	55.4% (46.1, 64.4)	69.5% (56.1, 80.8)
CR, n (%)	3 (1.7%)	2 (1.7%)	1 (1.7%)
PR, n (%)	105 (58.3%)	65 (53.7%)	40 (67.8%)
Duration of Response [Median (95% CI)]	9.69 months (6.93, 11.40)	7.39 months (5.42, 10.12)	NE[c] (5.55, NE)
Progression-free survival [Median (95% CI)]	6.97 months (6.21, 10.12)	6.90 months (5.39, 8.67)	NE[d] (6.67, NE)

[a] Response as assessed by the Investigator
[b] CR, PR confirmed
[c] Estimated DOR rate at 12 months was 71.1% (95% CI: 49.8, 84.6)
[d] Estimated PFS rate at 12 months was 58.1% (95% CI: 41.6, 71.5)
NE = Not estimable

Post-baseline tumor measurements were available for 169 patients with measurable disease at baseline out of the 180 response-evaluable patients. A waterfall plot displaying the maximum decrease from baseline in the sum of the longest tumor diameters shows that the majority of patients treated with Zykadia had a reduction in tumor burden (Figure 1).

Figure 1 - Best percentage change from baseline in sum of longest tumor diameters based on Investigator assessment in ALK-positive NSCLC patients from Zykadia 750 mg treatment dose group by prior ALK inhibitor status



Best percentage change from baseline<0 91.12% (154)
Best percentage change from baseline>0 3.55% (6)
Best percentage change from baseline=0 1.78% (3)
*% change in target lesion available but contradicted by overall lesion response = PD (contradicting assessment represents the only valid post-baseline assessment) 3.55% (6)
n (number of patients with measurable disease at baseline and at least one valid post-baseline assessment) is used for calculation of percentages.
A post-baseline assessment with unknown response for target lesion or unknown overall lesion response is considered invalid.
PFS event.

Subgroup analyses of ORR by region, age, gender, ethnicity, brain metastases at baseline, and disease burden at baseline did not reveal any meaningful differences in ORR (i.e., all differences in point estimate were ≤15% with overlapping 95% CIs). The ORR in patients with no brain metastases at baseline was 65.9% and in patients with brain metastases at baseline was 54.7%. An analysis of ORR by ECOG performance status showed a larger numerical difference in ORR: 73.5% in patients with ECOG performance status 0, and 55.0% in patients with ECOG performance status ≥1, but the 95% CIs for these two subgroups also overlap.

There were 11 ALK-positive NSCLC patients with Investigator-assessed measurable brain metastases at baseline enrolled in a clinical study of Zykadia. The overall intracranial response rate as assessed by the Investigator was 45.5% (95% CI: 16.7, 76.6) including 1 patient having a complete response in the brain and 4 patients with a confirmed partial response in the brain; in addition, 3 patients had stable disease.

NON-CLINICAL SAFETY DATA

Safety pharmacology

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 IC_{50} for the inhibitory effect of ceritinib on the hERG potassium channel was 0.4 micromolar at 33°C to 35°C (near body temperature). 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.

Genotoxicity

The Ames assay for ceritinib indicated it was not a potential mutagen, and the chromosomal aberration assay in cultured human peripheral blood lymphocytes did not indicate the potential to cause chromosomal aberrations. The micronucleus test using human peripheral blood lymphocytes was negative. An *in vivo* rat micronucleus test revealed no adverse effects on the bone marrow after oral dosing in the rat.

Carcinogenesis and Mutagenesis

Carcinogenicity studies have not been performed with ceritinib.

Pregnancy/fertility

Reproductive toxicology studies (i.e., embryo-fetal development 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 recommended dose of 750 mg in clinical trials. Formal non-clinical studies on the potential effects of ceritinib on fertility have not been conducted.

Repeated dose toxicity studies

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 characterized by body weight loss, decreased food consumption, emesis (monkey), diarrhea, and at high doses, by histopathologic lesions including erosion, mucosal inflammation, and foamy macrophages in the duodenal crypts and submucosa. Liver was also affected in both species, but only at the highest dose levels studied, 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.

STORAGE

Special precautions for storage

See folding box.

Zykadia should not be used after the date marked "EXP" on the pack.

Zykadia must be kept out of the reach and sight of children.

Manufacturer:

See folding box.

Further information is available from:

Novartis Healthcare Private Limited

Pharmaceuticals Division

Sandoz House, Shivsagar Estate,

Worli, Mumbai 400 018, India

Information issued : *India pack insert dtd 02 Apr 2014 based on IPL dtd 20 Feb 2014*

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