HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZYKADIA safely and effectively. See full prescribing information for ZYKADIA.

ZYKADIA® (ceritinib) capsules, for oral use
Initial U.S. Approval: 2014

----------INDICATIONS AND USAGE----------

ZYKADIA is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1)

----------DOSAGE AND ADMINISTRATION----------

- 750 mg orally once daily. Administer ZYKADIA on an empty stomach (i.e., do not administer within 2 hours of a meal). (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 150 mg (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Severe or Persistent Gastrointestinal Toxicity: Dose modification due to diarrhea, nausea, vomiting or abdominal pain occurred in 38% of patients. Withhold if not responsive to anti-emetics or anti-diarrheals, then dose reduce ZYKADIA. (2.2, 5.1)
- Hepatotoxicity: ZYKADIA can cause hepatotoxicity. Monitor liver laboratory tests at least monthly. Withhold then dose reduce, or permanently discontinue ZYKADIA. (2.2, 5.2)
- Interstitial Lung Disease (ILD)/Pneumonitis: Occurred in 4% of patients. Permanently discontinue ZYKADIA in patients diagnosed with treatment-related ILD/pneumonitis. (2.2, 5.3)
- QT Interval Prolongation: ZYKADIA can cause QTc interval prolongation. Monitor electrocardiograms and electrolytes in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or those who are taking medications that are known to prolong the QTc interval. Withhold then dose reduce, or permanently discontinue ZYKADIA. (2.2, 5.4)
- Hyperglycemia: ZYKADIA can cause hyperglycemia. Monitor fasting glucose prior to treatment and periodically thereafter as clinically indicated. Initiate or optimize anti-hyperglycemic medications as indicated. Withhold then dose reduce, or permanently discontinue ZYKADIA. (2.2, 5.5)
- Bradycardia: ZYKADIA can cause bradycardia. Monitor heart rate and blood pressure regularly. Withhold then dose reduce, or permanently discontinue ZYKADIA. (2.2, 5.6)
- Pancreatitis: Elevations of lipase and/or amylase and pancreatitis can occur. Monitor lipase and amylase prior to treatment and periodically thereafter as clinically indicated. (2.2, 5.7)
- Embryofetal Toxicity: ZYKADIA may cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus. (5.8, 8.1, 8.7)

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence of at least 25%) are diarrhea, nausea, elevated transaminases, vomiting, abdominal pain, fatigue, decreased appetite, and constipation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- CYP3A Inhibitors and Inducers: Avoid concurrent use of ZYKADIA with strong CYP3A inhibitors or inducers. If concurrent use of a strong CYP3A inhibitor is unavoidable, reduce the dose of ZYKADIA. (2.3, 7.1)
- CYP3A and CYP2C9 Substrates: Avoid concurrent use of ZYKADIA with CYP3A or CYP2C9 substrates with narrow therapeutic indices. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 9/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZYKADIA® is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

This indication is approved under accelerated approval based on tumor response rate and duration of response *[see Clinical Studies (14)]*. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing and Administration

The recommended dose of ZYKADIA is 750 mg orally once daily until disease progression or unacceptable toxicity. Administer ZYKADIA on an empty stomach (i.e., do not administer within 2 hours of a meal) *[see Clinical Pharmacology (12.3)]*.

A recommended dose has not been determined for patients with moderate to severe hepatic impairment *[see Use in Specific Populations (8.6)]*.

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

If vomiting occurs during the course of treatment, do not administer an additional dose and continue with the next scheduled dose of ZYKADIA.

2.2 Dose Modifications for Adverse Reactions

Recommendations for dose modifications of ZYKADIA for adverse reactions are provided in Table 1.

Approximately 58% of patients initiating treatment at the recommended dose required at least one dose reduction and the median time to first dose reduction was 7 weeks.

Discontinue ZYKADIA for patients unable to tolerate 300 mg daily.

Table 1: ZYKADIA Dose Interruption, Reduction, or Discontinuation Recommendations

Criteria	ZYKADIA Dosing
• ALT or AST elevation greater than 5 times ULN with • total bilirubin elevation **less than or equal to 2 times ULN**	Withhold until recovery to baseline or less than or equal to 3 times ULN, then resume ZYKADIA with a 150 mg dose reduction.
• ALT or AST elevation greater than 3 times ULN with • total bilirubin elevation **greater than 2 times ULN** in the absence of cholestasis or hemolysis	Permanently discontinue ZYKADIA.
Any Grade treatment-related ILD/pneumonitis	Permanently discontinue ZYKADIA.
QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then resume ZYKADIA with a 150 mg dose reduction.
QTc interval prolongation in combination with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue ZYKADIA.
Severe or intolerable nausea, vomiting or diarrhea despite optimal anti-emetic or anti-diarrheal therapy	Withhold until improved, then resume ZYKADIA with a 150 mg dose reduction.
Persistent hyperglycemia greater than 250 mg/dL despite optimal anti-hyperglycemic therapy	Withhold until hyperglycemia is adequately controlled, then resume ZYKADIA with a 150 mg dose reduction. If adequate hyperglycemic control cannot be achieved with optimal medical management, discontinue ZYKADIA.
Symptomatic bradycardia that is not life-threatening	Withhold until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, evaluate concomitant medications known to cause bradycardia, and adjust the dose of ZYKADIA.
Clinically significant bradycardia requiring intervention or life-threatening bradycardia in patients taking a concomitant medication also known to cause bradycardia or a medication known to cause hypotension	Withhold until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If the concomitant medication can be adjusted or discontinued, resume ZYKADIA with a 150 mg dose reduction, with frequent monitoring.
Life-threatening bradycardia in patients who are not taking a concomitant medication also known to cause bradycardia or known to cause hypotension	Permanently discontinue ZYKADIA.
Lipase or amylase elevation greater than 2 times ULN	Withhold and monitor serum lipase and amylase. Resume ZYKADIA with a 150 mg dose reduction after recovery to less than 1.5 times ULN.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; ILD, interstitial lung disease; ECG, electrocardiogram	

2.3 Dose Modification for Strong CYP3A4 Inhibitors

Avoid concurrent use of strong CYP3A inhibitors during treatment with ZYKADIA *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the ZYKADIA 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 ZYKADIA dose that was taken prior to initiating the strong CYP3A4 inhibitor.

3 DOSAGE FORMS AND STRENGTHS

150 mg hard gelatin capsule with opaque blue cap and opaque white body containing a white to off-white powder. The opaque blue cap is marked in black ink with “LDK 150MG” and the opaque white body is marked in black ink with “NVR”.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe or Persistent Gastrointestinal Toxicity

Diarrhea, nausea, vomiting, or abdominal pain occurred in 96% of 255 patients including severe cases in 14% of patients treated with ZYKADIA in Study 1. Dose modification due to diarrhea, nausea, vomiting, or abdominal pain occurred in 38% of patients.

Monitor and manage patients using standards of care, including antidiarrheals, antiemetics, or fluid replacement, as indicated. Based on the severity of the adverse drug reaction, withhold ZYKADIA with resumption at a reduced dose as described in Table 1 *[see Dosage and Administration (2.2) and Adverse Reactions (6)]*.

5.2 Hepatotoxicity

Drug-induced hepatotoxicity occurred in patients treated with ZYKADIA. Elevations in alanine aminotransferase (ALT) greater than 5 times the upper limit of normal (ULN) occurred in 27% of 255 patients in Study 1. One patient (0.4%) required permanent discontinuation due to elevated transaminases, and jaundice. Concurrent elevations in ALT greater than 3 times the ULN and total bilirubin greater than 2 times the ULN, with normal alkaline phosphatase, occurred in less than 1% of patients in clinical studies.

Monitor with liver laboratory tests including ALT, aspartate aminotransferase (AST), and total bilirubin once a month and as clinically indicated, with more frequent testing in patients who develop transaminase elevations. Based on the severity of the adverse drug reaction, withhold ZYKADIA with resumption at a reduced dose, or permanently discontinue ZYKADIA as described in Table 1 *[see Dosage and Administration (2.2) and Adverse Reactions (6)]*.

5.3 Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, or fatal ILD/pneumonitis can occur in patients treated with ZYKADIA. In Study 1, pneumonitis was reported in 4% of 255 patients treated with ZYKADIA. CTCAE Grade 3 or 4 ILD/pneumonitis was reported in 3% of patients, and fatal ILD/pneumonitis was reported in 1 patient (0.4%) in Study 1. One percent (1%) of patients discontinued ZYKADIA in Study 1 due to ILD/pneumonitis.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Exclude other potential causes of ILD/pneumonitis, and permanently discontinue ZYKADIA in patients diagnosed with treatment-related ILD/pneumonitis *[see Dosage and Administration (2.2) and Adverse Reactions (6)]*.

5.4 QT Interval Prolongation

QTc interval prolongation, which may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade de pointes) or sudden death, occurred in patients treated with ZYKADIA in clinical trials. Three percent (3%) of 255 patients experienced a QTc interval increase over baseline greater than 60 msec in Study 1. Across the development program of ZYKADIA, one of 304 patients (less than 1%) treated with ZYKADIA doses ranging from 50 to 750 mg was found to have a QTc greater than 500 msec and 3% of patients had an increase from baseline QTc greater than 60 msec. A pharmacokinetic analysis suggested that ZYKADIA causes concentration-dependent increases in the QTc interval.

When possible, avoid use of ZYKADIA in patients with congenital long QT syndrome. Conduct periodic monitoring with electrocardiograms (ECGs) and electrolytes in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or those who are taking medications that are known to prolong the QTc interval. Withhold ZYKADIA in patients who develop a QTc interval greater than 500 msec on at least 2 separate ECGs until the QTc interval is less than 481 msec or recovery to baseline if the QTc interval is greater than or equal to 481 msec, then resume ZYKADIA at a reduced dose as described in Table 1. Permanently discontinue ZYKADIA in patients who develop QTc interval prolongation in combination with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.2)]*.

5.5 Hyperglycemia

Hyperglycemia can occur in patients receiving ZYKADIA. In Study 1, CTCAE Grade 3–4 hyperglycemia, based on laboratory values, occurred in 13% of 255 patients. There was a 6-fold increase in the risk of CTCAE Grade 3–4 hyperglycemia in patients with diabetes or glucose intolerance and a 2-fold increase in patients taking corticosteroids.

Monitor fasting serum glucose prior to the start of ZYKADIA treatment and periodically thereafter as clinically indicated. Initiate or optimize antihyperglycemic medications as indicated. Based on the severity of the adverse drug reaction, withhold ZYKADIA until hyperglycemia is adequately controlled, then resume ZYKADIA at a reduced dose as described in Table 1. If adequate hyperglycemic control cannot be achieved with optimal medical management, permanently discontinue ZYKADIA *[see Dosage and Administration (2.2) and Adverse Reactions (6)]*.

5.6 Bradycardia

Bradycardia can occur in patients receiving ZYKADIA. In Study 1, sinus bradycardia, defined as a heart rate of less than 50 beats per minute, was noted as a new finding in 1% of 255 patients. Bradycardia was reported as an adverse drug reaction in 3% of patients in Study 1.

Avoid using 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. Permanently discontinue ZYKADIA for life-threatening bradycardia if no contributing concomitant medication is identified; however, if associated with a 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 the concomitant medication can be adjusted or discontinued, resume ZYKADIA at a reduced dose as described in Table 1 upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring *[see Dosage and Administration (2.2) and Adverse Reactions (6)]*.

5.7 Pancreatitis

Pancreatitis, including one fatality, has been reported in less than 1% of patients receiving ZYKADIA in clinical trials. CTCAE Grade 3-4 elevations of lipase and/or amylase occurred in 15% of patients receiving ZYKADIA in Study 1. Monitor lipase and amylase prior to the start of ZYKADIA treatment and periodically thereafter as clinically indicated. Based on the severity of the laboratory abnormalities, withhold ZYKADIA with resumption at a reduced dose as described in Table 1 *[see Dosage and Administration (2.2) and Adverse Reactions (6)]*.

5.8 Embryofetal Toxicity

Based on its mechanism of action, ZYKADIA may cause fetal harm when administered to a pregnant woman. In animal studies, administration of ceritinib to rats and rabbits during organogenesis at maternal plasma exposures below the recommended human dose of 750 mg daily caused increases in skeletal anomalies in rats and rabbits. Apprise women of reproductive potential of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with ZYKADIA and for at least 2 weeks following completion of therapy *[see Use in Specific Populations (8.7)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Severe or Persistent Gastrointestinal Toxicity *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.2)]*
- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.3)]*
- QT Interval Prolongation *[see Warnings and Precautions (5.4) and Clinical Pharmacology (12.2)]*
- Hyperglycemia *[see Warnings and Precautions (5.5)]*
- Bradycardia *[see Warnings and Precautions (5.6) and Clinical Pharmacology (12.2)]*
- Pancreatitis *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety evaluation of ZYKADIA is based on 255 ALK-positive patients in Study 1 (246 patients with NSCLC and 9 patients with other cancers who received ZYKADIA at a dose of 750 mg daily). The median duration of exposure to ZYKADIA was 6 months. The study population characteristics were: median age 53 years, age less than 65 (84%), female (53%), Caucasian (63%), Asian (34%), NSCLC adenocarcinoma histology (90%), never or former smoker (97%), ECOG PS 0 or 1 (89%), brain metastasis (49%), and number of prior therapies 2 or more (67%).

Dose reductions due to adverse reactions occurred in 59% of patients treated with ZYKADIA. The most frequent adverse reactions, reported in at least 10% of patients, that led to dose reductions or interruptions were: increased ALT (29%), nausea (20%), increased AST (16%), diarrhea (16%), and vomiting (16%). Serious adverse drug reactions reported in 2% or more of patients in Study 1 were convulsion, pneumonia, ILD/pneumonitis, dyspnea, dehydration, hyperglycemia, and nausea. Fatal adverse reactions in patients treated with ZYKADIA occurred in 5% of patients, consisting of: pneumonia (4 patients), respiratory failure, ILD/pneumonitis, pneumothorax, gastric hemorrhage, general physical health deterioration, pulmonary tuberculosis, cardiac tamponade, and sepsis (1 patient each). Discontinuation of therapy due to adverse reactions occurred in 10% of patients treated with ZYKADIA. The most frequent adverse drug reactions that led to discontinuation in 1% or more of patients in Study 1 were pneumonia, ILD/pneumonitis, and decreased appetite.

Tables 2 and 3 summarize the common adverse reactions and laboratory abnormalities observed in ZYKADIA-treated patients.

Table 2: Adverse Reactions (>10% for All NCI CTCAE* Grades or ≥2% for Grades 3-4) in ALK-Positive Patients Treated with ZYKADIA in Study 1

	ZYKADIA N=255	
	All Grades	**Grade 3–4**
	%	**%**
Gastrointestinal disorders		
Diarrhea	86	6
Nausea	80	4
Vomiting	60	4
Abdominal pain[a]	54	2
Constipation	29	0
Esophageal disorder[b]	16	1
General disorders and administration site conditions		
Fatigue[c]	52	5
Metabolism and nutrition disorders		
Decreased appetite	34	1
Skin and subcutaneous tissue disorders		
Rash[d]	16	0
Respiratory, thoracic and mediastinal disorders		
Interstitial lung disease/pneumonitis	4	3

*National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03)
[a]Abdominal pain (abdominal pain, upper abdominal pain, abdominal discomfort, epigastric discomfort)
[b]Esophageal disorder (dyspepsia, gastroesophageal reflux disease, dysphagia)
[c]Fatigue (fatigue, asthenia)
[d]Rash (rash, maculopapular rash, acneiform dermatitis)

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ZYKADIA included neuropathy (17%; comprised of paresthesia, muscular weakness, gait disturbance, peripheral neuropathy, hypoesthesia, peripheral sensory neuropathy, dysesthesia, neuralgia, peripheral motor neuropathy, hypotonia, or polyneuropathy), vision disorder (9%; comprised of vision impairment, blurred vision, photopsia, accommodation disorder, presbyopia, or reduced visual acuity), prolonged QT interval (4%), and bradycardia (3%).

Table 3: Key Laboratory Abnormalities Occurring in >10% (All NCI CTCAE Grades) of ALK-Positive Patients Treated with ZYKADIA in Study 1

	ZYKADIA N=255	
	All Grades	**Grade 3–4**
	%	**%**
Hemoglobin decreased	84	5
Alanine transaminase (ALT) increased	80	27
Aspartate transaminase (AST) increased	75	13
Creatinine increased	58	2
Glucose increased	49	13
Phosphate decreased	36	7
Lipase increased	28	10
Bilirubin (total) increased	15	1

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Ceritinib

Ceritinib is primarily metabolized by CYP3A4 and is a substrate of the efflux transporter P-glycoprotein (P-gp).

Strong CYP3A Inhibitors

A strong CYP3A4/P-gp inhibitor (ketoconazole) increased the systemic exposure of ceritinib *[see Clinical Pharmacology (12.3)]*. Avoid concurrent use of strong CYP3A inhibitors during treatment with ZYKADIA. If concomitant use of strong CYP3A inhibitors including certain antivirals (e.g., ritonavir), macrolide antibiotics (e.g., telithromycin), antifungals (e.g., ketoconazole), and nefazodone is unavoidable, reduce the ZYKADIA 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 ZYKADIA dose that was taken prior to initiating the strong CYP3A4 inhibitor.

Do not consume grapefruit and grapefruit juice as they may inhibit CYP3A.

Strong CYP3A Inducers

A strong CYP3A4/P-gp inducer (rifampin) decreased the systemic exposure of ceritinib *[see Clinical Pharmacology (12.3)]*. Avoid concurrent use of strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, and St. John's Wort) during treatment with ZYKADIA.

7.2 Effect of Ceritinib on Other Drugs

Ceritinib may inhibit CYP3A and CYP2C9 at clinical concentrations *[see Clinical Pharmacology (12.3)]*. Avoid concurrent use of CYP3A and CYP2C9 substrates known to have narrow therapeutic indices or substrates primarily metabolized by CYP3A and CYP2C9 during treatment with ZYKADIA. If use of these medications is unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus) and CYP2C9 substrates with narrow therapeutic indices (e.g., phenytoin, warfarin).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Risk Summary

Based on its mechanism of action, ZYKADIA may cause fetal harm when administered to a pregnant woman. In animal studies, administration of ceritinib to rats and rabbits during organogenesis at maternal plasma exposures below the recommended human dose caused increases in skeletal anomalies in rats and rabbits. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.

Animal Data

In an embryo-fetal development study in which pregnant rats were administered daily doses of ceritinib during organogenesis, dose-related skeletal anomalies were observed at doses as low as 50 mg/kg (less than 0.5-fold the human exposure by AUC at the recommended dose). Findings included delayed ossifications and skeletal variations.

In pregnant rabbits administered ceritinib daily during organogenesis, dose-related skeletal anomalies, including incomplete ossification, were observed at doses equal to or greater than 2 mg/kg/day (approximately 0.015-fold the human exposure by AUC at the recommended dose). A low incidence of visceral anomalies, including absent or malpositioned gallbladder and retroesophageal subclavian cardiac artery, was observed at doses equal to or greater than 10 mg/kg/day (approximately 0.13-fold the human exposure by AUC at the recommended dose). Maternal toxicity and abortion occurred in rabbits at doses of 35 mg/kg or greater. In addition, embryolethality was observed in rabbits at a dose of 50 mg/kg.

8.3 Nursing Mothers

It is not known whether ceritinib or its metabolites are present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from ceritinib, advise mothers to discontinue nursing.

8.4 Pediatric Use

The safety and effectiveness of ZYKADIA in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of ZYKADIA did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. Of the 255 patients in Study 1 who received ZYKADIA at the recommended dose, 40 (16%) were 65 years or older.

8.6 Hepatic Impairment

As ceritinib is eliminated primarily via the liver, patients with hepatic impairment may have increased exposure. Dose adjustment is not recommended for patients with mild hepatic impairment (total bilirubin less than or equal to ULN and AST greater than ULN or total bilirubin greater than 1.0 to 1.5 times ULN and any AST) based on results of the population pharmacokinetic analysis *[see Clinical Pharmacology (12.3)]*. A recommended dose has not been determined for patients with moderate to severe hepatic impairment.

8.7 Females and Males of Reproductive Potential

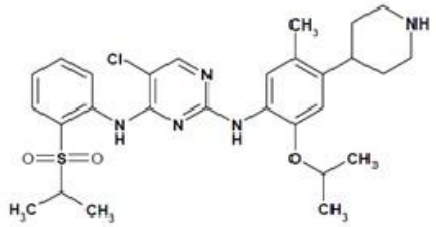
Contraception

Based on its mechanism of action, ZYKADIA may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with ZYKADIA and for at least 2 weeks following completion of therapy.

11 DESCRIPTION

ZYKADIA (ceritinib) is a tyrosine kinase inhibitor for oral administration. The molecular formula for ceritinib is $C_{28}H_{36}N_5O_3ClS$. The molecular weight is 558.14 g/mole. Ceritinib is described chemically as 5-Chloro-N4-[2-[(1-methylethyl)sulfonyl]phenyl]-N2-[5-methyl-2-(1-methylethoxy)-4-(4-piperidinyl)phenyl]-2,4-pyrimidinediamine.

The chemical structure of ceritinib is shown below:



Ceritinib is a white to almost white or light yellow or light brown powder with a pKa of 9.7 and 4.1.

ZYKADIA is supplied as printed hard-gelatin capsules containing 150 mg of ceritinib and the following inactive ingredients: colloidal anhydrous silica, L-hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and hard gelatin capsule shells. The capsule shell is composed of gelatin, indiogotine, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ceritinib is a kinase inhibitor. Targets of ceritinib inhibition identified in either biochemical or cellular assays at clinically relevant concentrations include ALK, insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and ROS1. Among these, ceritinib is most active against ALK. Ceritinib inhibited autophosphorylation of ALK, ALK-mediated phosphorylation of the downstream signaling protein STAT3, and proliferation of ALK-dependent cancer cells in in vitro and in vivo assays.

Ceritinib inhibited the in vitro proliferation of cell lines expressing EML4-ALK and NPM-ALK fusion proteins and demonstrated dose-dependent inhibition of EML4-ALK-positive NSCLC xenograft growth in mice and rats. Ceritinib exhibited dose-dependent anti-tumor activity in mice bearing EML4-ALK-positive NSCLC xenografts with demonstrated resistance to crizotinib, at concentrations within a clinically relevant range.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of ceritinib on the QT interval in an open-label, dose-escalation, and expansion study. A total of 304 patients were treated with ZYKADIA doses ranging from 50 to 750 mg with 255 patients treated with ZYKADIA 750 mg. One of 304 patients (less than 1%) was found to have a QTc greater than 500 msec and 10 patients (3%) had an increase from baseline QTc greater than 60 msec. A central tendency analysis of the QTc data at average steady-state concentrations demonstrated that the upper bound of the 2-sided 90% CI for QTc was 16 msec at ZYKADIA 750 mg. A pharmacokinetic/pharmacodynamic analysis suggested concentration-dependent QTc interval prolongation *[see Warnings and Precautions (5.4)]*.

Based on central review of ECG data, 2 of 304 patients (0.7%) had bradycardia defined as less than 50 beats per minute. Bradycardia was reported as an adverse drug reaction in 3% of patients in Study 1.

12.3 Pharmacokinetics

Absorption

After single oral administration of ZYKADIA in patients, peak plasma levels (C_{max}) of ceritinib were achieved at approximately 4 to 6 hours, and area under the curve (AUC) and C_{max} increased dose proportionally over 50 to 750 mg. The absolute bioavailability of ZYKADIA has not been determined.

Following ZYKADIA 750 mg once daily dosing, steady-state was reached by approximately 15 days with a geometric mean accumulation ratio of 6.2 after 3 weeks. Systemic exposure increased in a greater than dose proportional manner after repeat doses of 50 to 750 mg once daily.

Systemic exposure of ceritinib was increased when administered with a meal. A food effect study conducted in healthy subjects with a single 500 mg ceritinib dose showed that a high-fat meal (containing approximately 1000 calories and 58 grams of fat) increased ceritinib AUC by 73% and C_{max} by 41% and a low-fat meal (containing approximately 330 calories and 9 grams of fat) increased ceritinib AUC by 58% and C_{max} by 43% as compared with the fasted state. A 600

mg or higher ZYKADIA dose taken with a meal is expected to result in systemic exposure exceeding that of a 750 mg ZYKADIA dose taken in the fasted state, and may increase adverse drug reactions.

Distribution

Ceritinib is 97% bound to human plasma proteins, independent of drug concentration. The apparent volume of distribution (V_d/F) is 4230 L following a single 750 mg ZYKADIA dose in patients. 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.

Elimination

Following a single 750 mg ZYKADIA dose, the geometric mean apparent plasma terminal half-life ($t_{1/2}$) of ceritinib was 41 hours in patients. Ceritinib demonstrates nonlinear PK over time. The geometric mean apparent clearance (CL/F) of ceritinib was lower at steady-state (33.2 L/h) after 750 mg daily dosing than after a single 750 mg dose (88.5 L/h).

Metabolism: In vitro studies demonstrated that CYP3A was the major enzyme involved in the metabolic clearance of ceritinib. Following oral administration of a single 750 mg radiolabeled ceritinib dose, ceritinib as the parent compound was the main circulating component (82%) in human plasma.

Excretion: Following oral administration of a single 750 mg radiolabeled ceritinib dose, 92.3% of the administered dose was recovered in the feces (with 68% as unchanged parent compound) while 1.3% of the administered dose was recovered in the urine.

Specific Populations

Age, Gender, Race, and Body Weight: Age, gender, race, and body weight had no clinically important effect on the systemic exposure of ceritinib based on population pharmacokinetic analyses.

Hepatic Impairment: As ceritinib is eliminated primarily via the liver, patients with hepatic impairment may have increased exposure. A pharmacokinetic trial in patients with hepatic impairment has not been conducted. Based on a population pharmacokinetic analysis of 48 patients with mild hepatic impairment (total bilirubin less than or equal to ULN and AST greater than ULN or total bilirubin greater than 1.0 to 1.5 times ULN and any AST) and 254 patients with normal hepatic function (total bilirubin less than or equal to ULN and AST less than or equal to ULN), ceritinib exposures were similar in patients with mild hepatic impairment and normal hepatic function. The pharmacokinetics of ceritinib has not been studied in patients with moderate to severe hepatic impairment *[see Use in Specific Populations (8.6)]*.

Renal Impairment: A pharmacokinetic trial in patients with renal impairment has not been conducted as ceritinib elimination via the kidney is low (1.3% of a single oral administered dose). Based on a population pharmacokinetic analysis of 97 patients with mild renal impairment (CLcr 60 to less than 90 mL/min), 22 patients with moderate renal impairment (CLcr 30 to less than 60 mL/min) and 183 patients with normal renal function (greater than or equal to 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 less than 30 mL/min) were not included in the clinical trial.

Pediatrics: No trials have been conducted to evaluate the pharmacokinetics of ceritinib in pediatric patients.

Drug Interactions

Effect of Strong CYP3A Inhibitors on Ceritinib: In vitro studies show that ceritinib is a substrate of CYP3A. Coadministration of a single 450 mg ZYKADIA dose with ketoconazole (a strong CYP3A inhibitor) 200 mg twice daily for 14 days increased ceritinib AUC (90% CI) by 2.9-fold (2.5, 3.3) and C_{max} (90% CI) by 22% (7%, 39%) in 19 healthy subjects *[see Drug Interactions (7.1)]*. The steady-state AUC of ceritinib at reduced doses after coadministration with ketoconazole 200 mg twice daily for 14 days was predicted by simulations to be similar to the steady-state AUC of ceritinib alone *[see Dosage and Administration (2.3)]*.

Effect of Strong CYP3A Inducers on Ceritinib: Coadministration of a single 750 mg ZYKADIA dose with rifampin (a strong CYP3A inducer) 600 mg daily for 14 days decreased ceritinib AUC (90% CI) by 70% (61%, 77%) and C_{max} (90% CI) by 44% (24%, 59%) in 19 healthy subjects *[see Drug Interactions (7.1)]*.

Effect of Ceritinib on CYP Substrates: Based on in vitro data, ceritinib may inhibit CYP3A and CYP2C9 at clinical concentrations *[see Drug Interactions (7.2)]*. Time-dependent inhibition of CYP3A was also observed.

Effect of Transporters on Ceritinib Disposition: Ceritinib is a substrate of efflux transporter P-gp, but is not a substrate of Breast Cancer Resistance Protein (BCRP), Multidrug Resistance Protein (MRP2), Organic Cation Transporter (OCT1), Organic Anion Transporter (OAT2), or Organic Anion Transporting Polypeptide (OATP1B1) in vitro. Drugs that inhibit P-gp may increase ceritinib concentrations.

Effect of Ceritinib on Transporters: Based on in vitro data, ceritinib does not inhibit apical efflux transporters, P-gp, BCRP, or MRP2, hepatic uptake transporters OATP1B1 and OATP1B3, renal organic anion uptake transporters OAT1 and OAT3, or organic cation uptake transporters OCT1 and OCT2 at clinical concentrations.

Effect of Acid Reducing Agents on Ceritinib: 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. Coadministration of a single 750 mg ZYKADIA dose with a proton pump inhibitor (esomeprazole) 40 mg daily for 6 days in healthy subjects decreased ceritinib AUC (90% CI) by 76% (66%, 83%) and C_{max} (90% CI) by 79% (70%, 86%). However, coadministration of a single 750 mg ZYKADIA dose with proton pump inhibitors for 6 days in a subgroup of patients from Study 1 suggested less effect on ceritinib exposure than that observed in healthy subjects as AUC (90% CI) decreased by 30% (0%, 52%) and C_{max} (90% CI) decreased by 25% (5%, 41%) and no clinically meaningful effect on ceritinib exposure was observed at steady-state after ZYKADIA once daily dosing.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with ceritinib.

Ceritinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay but induced numerical aberrations (aneugenic) in the in vitro cytogenetic assay using human lymphocytes, and micronuclei in the in vitro micronucleus test using TK6 cells. Ceritinib was not clastogenic in the in vivo rat micronucleus assay.

There are no data on the effect of ceritinib on human fertility. Fertility/early embryonic development studies were not conducted with ceritinib. There were no adverse effects on male or female reproductive organs in general toxicology studies conducted in monkeys and rats at exposures equal to or greater than 0.5- and 1.5-fold, respectively, of the human exposure by AUC at the recommended dose of 750 mg.

13.2 Animal Toxicology and/or Pharmacology

Target organs in nonclinical animal models included, but were not limited to, the pancreas, biliopancreatic/bile ducts, gastrointestinal tract, and liver. Pancreatic focal acinar cell atrophy was observed in rats at 1.5-fold the human exposure by AUC at the recommended dose. Biliopancreatic duct and bile duct necrosis was observed in rats at exposures equal to or greater than 5% of the human exposure by AUC at the recommended dose. Bile duct inflammation and vacuolation were also noted in monkeys at exposures equal to or greater than 0.5-fold the human exposure by AUC at the recommended dose. Frequent minimal necrosis and hemorrhage of the duodenum was exhibited in monkeys at 0.5-fold the human exposure by AUC, and in rats at an exposure similar to that observed clinically.

Ceritinib crossed the blood brain barrier in rats with a brain-to-blood exposure (AUC_{inf}) ratio of approximately 15%.

14 CLINICAL STUDIES

The efficacy of ZYKADIA was established in a multicenter, single-arm, open-label clinical trial (Study 1). A total of 163 patients with metastatic ALK-positive NSCLC who progressed while receiving or were intolerant to crizotinib were enrolled. All patients received ZYKADIA at a dose of 750 mg once daily. The major efficacy outcome measure was objective response rate (ORR) according to RECIST v1.0 as evaluated by both investigators and a Blinded Independent Central Review Committee (BIRC). Duration of response (DOR) was an additional outcome measure.

The study population characteristics were: median age 52 years, age less than 65 (87%), female (54%), Caucasian (66%), Asian (29%), never or former smoker (97%), ECOG PS 0 or 1 (87%), progression on previous crizotinib (91%), number of prior therapies 2 or more (84%), and adenocarcinoma histology (93%). Sites of extra-thoracic metastasis included brain (60%), liver (42%), and bone (42%). ALK-positivity was verified retrospectively by review of local test results for 99% of patients.

Efficacy results from Study 1 are summarized in Table 4.

Table 4: Overall Response Rate and Duration of Response[1] in Patients with ALK-Positive NSCLC who Received Prior Crizotinib in Study 1

Efficacy Parameter	Investigator Assessment (N=163)	BIRC Assessment (N=163)
Overall Response Rate (95% CI)	54.6% (47, 62)	43.6% (36, 52)
CR	1.2%	2.5%
PR	53.4%	41.1%
Duration of Response, median (months) (95% CI)	7.4 (5.4, 10.1)	7.1 (5.6, NE)

[1]Overall Response Rate and Duration of Response determined by RECIST v1.0
BIRC, blinded independent review committee; CR, complete response; NE, not estimable; PR, partial response.

The analysis by the BIRC assessment was similar to the analysis by the investigator assessment.

16 HOW SUPPLIED/STORAGE AND HANDLING

ZYKADIA 150 mg capsules

Hard gelatin capsule with opaque blue cap and opaque white body; opaque blue cap marked in black ink with “LDK 150MG”, opaque white body marked in black ink with “NVR”. Available in:

Bottles of 70 capsules…….NDC 0078-0640-70

Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- Inform patients that diarrhea, nausea, vomiting, and abdominal pain are the most commonly reported adverse reactions in patients treated with ZYKADIA. Inform patients of supportive care options such as anti-emetic and anti-diarrheal medications. Advise patients to contact their healthcare provider for severe or persistent gastrointestinal symptoms. Inform patients that if vomiting occurs during the course of treatment, they should not take an additional dose, but should continue with the next scheduled dose of ZYKADIA *[see Warnings and Precautions (5.1)]*.
- Inform patients of the signs and symptoms of hepatotoxicity. Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatotoxicity *[see Warnings and Precautions (5.2)]*.
- Inform patients of the risks of severe or fatal ILD/pneumonitis. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms *[see Warnings and Precautions (5.3)]*.
- Inform patients of the risks of QTc interval prolongation and bradycardia. Advise patients to contact their healthcare provider immediately to report new chest pain or discomfort, changes in heartbeat, palpitations, dizziness, lightheadedness, fainting, and changes in or new use of heart or blood pressure medications *[see Warnings and Precautions (5.4, 5.6)]*.
- Inform patients of the signs and symptoms of hyperglycemia. Advise patients to contact their healthcare provider immediately for signs or symptoms of hyperglycemia *[see Warnings and Precautions (5.5)]*.
- Inform patients of the signs and symptoms of pancreatitis and the need to monitor lipase and amylase levels prior to the start of treatment and periodically thereafter as clinically indicated *[see Warnings and Precautions (5.7)]*.
- Advise females to inform their healthcare provider if they are pregnant. Inform females of reproductive potential of the risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYKADIA and for at least 2 weeks following completion of therapy *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1, 8.7)]*.
- Advise females not to breastfeed during treatment with ZYKADIA *[see Use in Specific Populations (8.3)]*.

- Inform patients not to consume grapefruit and grapefruit juice during treatment with ZYKADIA *[see Drug Interactions (7.1)]*.
- Take ZYKADIA on an empty stomach (i.e., do not take within 2 hours of a meal) *[see Dosage and Administration (2.1)]*.
- Advise patients to make up a missed dose of ZYKADIA unless the next dose is due within 12 hours *[see Dosage and Administration (2.1)]*.

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PATIENT INFORMATION

ZYKADIA® (zye kaye' dee ah)

(ceritinib) capsules

What is the most important information I should know about ZYKADIA?

ZYKADIA may cause serious side effects, including:

Stomach and intestinal (gastrointestinal) problems. ZYKADIA causes stomach and intestinal problems in most people, including diarrhea, nausea, vomiting, and stomach-area pain. These problems can sometimes be severe. Follow your healthcare provider's instructions about taking medicines to help these symptoms. Call your healthcare provider for advice if your symptoms are severe or do not go away.

Liver problems. ZYKADIA may cause liver injury. Your healthcare provider should do blood tests at least every month to check your liver while you are taking ZYKADIA. Tell your healthcare provider right away if you get any of the following:

- you feel tired
- your skin or the whites of your eyes turn yellow
- you have a decreased appetite
- your urine turns dark or brown (tea color)
- you have itchy skin
- you have nausea or vomiting
- you have pain on the right side of your stomach-area
- you bleed or bruise more easily than normal

Lung problems (pneumonitis). ZYKADIA may cause severe or life-threatening inflammation of the lungs during treatment that can lead to death. Symptoms may be similar to those symptoms from lung cancer. Tell your healthcare provider right away if you have any new or worsening symptoms, including:

- trouble breathing or shortness of breath
- fever
- cough with or without mucous
- chest pain

Heart problems. ZYKADIA may cause very slow, very fast, or abnormal heartbeats. Your healthcare provider may check your heart during treatment with ZYKADIA. Tell your healthcare provider right away if you feel new chest pain or discomfort, dizziness or lightheadedness, if you faint, or have abnormal heartbeats. Tell your healthcare provider if you start to take or have any changes in heart or blood pressure medicines.

See "What are possible side effects of ZYKADIA?" for more information about side effects.

What is ZYKADIA?

ZYKADIA is a prescription medicine that is used to treat people with non-small cell lung cancer (NSCLC) that:

- is caused by a defect in a gene called anaplastic lymphoma kinase (ALK), and
- has spread to other parts of the body, and
- who have taken the medicine crizotinib, but their NSCLC worsened or they cannot tolerate taking crizotinib.

It is not known if ZYKADIA is safe and effective in children.

What should I tell my healthcare provider before taking ZYKADIA?

Before you take ZYKADIA, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems
- have diabetes or high blood sugar
- have heart problems, including a condition called long QT syndrome
- have or have had pancreatitis
- are pregnant or plan to become pregnant. ZYKADIA may harm your unborn baby. Females who are able to become pregnant should use an effective method of birth control during treatment with ZYKADIA and for at least 2 weeks after stopping ZYKADIA. Talk to your healthcare provider about birth control methods that may be right for you.
- are breastfeeding or plan to breastfeed. It is not known if ZYKADIA passes into your breast milk. You should not breastfeed if you take ZYKADIA.

Tell your healthcare provider about all the medicines you take, including prescription medicines, over-the-counter medicines, vitamins, and herbal supplements.

How should I take ZYKADIA?

- Take ZYKADIA exactly as your healthcare provider tells you. Do not change your dose or stop taking unless your healthcare provider tells you to.
- Take ZYKADIA 1 time each day.
- Take ZYKADIA on an empty stomach, do not eat for 2 hours before and do not eat for 2 hours after taking ZYKADIA.
- If you vomit after taking ZYKADIA, do not take an additional dose, but continue with the next scheduled dose.
- If you miss a dose of ZYKADIA, take it as soon as you remember. If your next dose is due within 12 hours, then skip the missed dose. Just take the next dose at your regular time.

What should I avoid while taking ZYKADIA?

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

What are the possible side effects of ZYKADIA?

ZYKADIA may cause serious side effects, including:

- **See "What is the most important information I should know about ZYKADIA?"**
- **High blood sugar (hyperglycemia).** People who have diabetes or glucose intolerance or who take a corticosteroid medicine have an increased risk of high blood sugar with ZYKADIA. Your healthcare provider will check your blood sugar level before starting ZYKADIA and as needed during treatment with ZYKADIA. Call your healthcare provider right away if you have any symptoms of high blood sugar, including:
  - increased thirst
  - increased hunger
  - headaches
  - trouble thinking or concentrating
  - urinating often
  - blurred vision
  - tiredness
  - your breath smells like fruit
- **Inflammation of the pancreas (pancreatitis).** Zykadia can cause pancreatitis that has led to death. You may develop increased pancreatic enzyme blood levels, which may be a sign of pancreatitis. Signs and symptoms of pancreatitis include upper abdominal pain that may

spread to the back and get worse with eating. Your healthcare provider should do blood tests to check your pancreatic enzyme blood levels before you start ZYKADIA and as needed during your treatment.

The most common side effects of ZYKADIA include:

- stomach and intestinal (gastrointestinal) problems. **See "What is the most important information I should know about ZYKADIA?"**
- tiredness, decreased appetite, and constipation

These are not all of the possible side effects of ZYKADIA. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZYKADIA?

- Store ZYKADIA at room temperature between 68°F to 77°F (20°C to 25°C).

Keep ZYKADIA and all medicines out of the reach of children.

General information about the safe and effective use of ZYKADIA

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ZYKADIA for a condition for which it was not prescribed. Do not give it to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for more information about ZYKADIA.

What are the ingredients in ZYKADIA?

Active ingredient: ceritinib

Inactive ingredients: colloidal anhydrous silica, L-hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate

Capsule shell contains: gelatin, indiogotine, and titanium dioxide

Distributed by: Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936
For more information, go to www.US.ZYKADIA.com or call 888-669-6682.

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