

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 metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. (1)

DOSAGE AND ADMINISTRATION

450 mg orally once daily with food. (2.2)

DOSAGE FORMS AND STRENGTHS

Capsules: 150 mg (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- **Gastrointestinal Adverse Reactions:** ZYKADIA can cause gastrointestinal adverse reactions. If severe or intolerable, withhold if not responsive to antiemetics or antidiarrheals, then dose reduce ZYKADIA. (2.3, 5.1)
- **Hepatotoxicity:** ZYKADIA can cause hepatotoxicity. Monitor liver laboratory tests at least monthly. Withhold then dose reduce, or permanently discontinue ZYKADIA. (2.3, 5.2)
- **Interstitial Lung Disease (ILD)/Pneumonitis:** Occurred in 2.4% of patients. Permanently discontinue ZYKADIA in patients diagnosed with treatment-related ILD/pneumonitis. (2.3, 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. (2.3, 5.4)
- **Hyperglycemia:** ZYKADIA can cause hyperglycemia. Monitor fasting glucose prior to treatment and periodically thereafter as clinically indicated.

- Initiate or optimize antihyperglycemic medications as indicated. Withhold then dose reduce, or permanently discontinue ZYKADIA. (2.3, 5.5)
- **Bradycardia:** ZYKADIA can cause bradycardia. Monitor heart rate and blood pressure regularly. Withhold then dose reduce, or permanently discontinue ZYKADIA. (2.3, 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. (2.3, 5.7)
- **Embryo-Fetal Toxicity:** ZYKADIA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.8, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (incidence of at least 25%) in patients treated with ZYKADIA 750 mg fasted are diarrhea, nausea, fatigue, vomiting, abdominal pain, decreased appetite, and weight loss. (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. (2.4, 7.1)
- **CYP3A Substrates:** Avoid coadministration of ZYKADIA with sensitive CYP3A substrates. (7.2)
- **CYP2C9 Substrates:** Avoid coadministration of ZYKADIA with CYP2C9 substrates for which minimal concentration changes may lead to serious toxicities. (7.2)

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

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

Revised: 3/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

| | |
|----------|---|
| 1 | INDICATIONS AND USAGE |
| 2 | DOSAGE AND ADMINISTRATION |
| 2.1 | Patient Selection |
| 2.2 | Dosing and Administration |
| 2.3 | Dose Modifications for Adverse Reactions |
| 2.4 | Dose Modification for Strong CYP3A Inhibitors |
| 2.5 | Dose Modification for Patients with Severe Hepatic Impairment |
| 3 | DOSAGE FORMS AND STRENGTHS |
| 4 | CONTRAINDICATIONS |
| 5 | WARNINGS AND PRECAUTIONS |
| 5.1 | Gastrointestinal Adverse Reactions |
| 5.2 | Hepatotoxicity |
| 5.3 | Interstitial Lung Disease (ILD)/Pneumonitis |
| 5.4 | QT Interval Prolongation |
| 5.5 | Hyperglycemia |
| 5.6 | Bradycardia |
| 5.7 | Pancreatitis |
| 5.8 | Embryo-Fetal Toxicity |
| 6 | ADVERSE REACTIONS |
| 6.1 | Clinical Trials Experience |
| 7 | DRUG INTERACTIONS |
| 7.1 | Effect of Other Drugs on Ceritinib |

| | |
|-----------|--|
| 7.2 | Effect of Ceritinib on Other Drugs |
| 8 | USE IN SPECIFIC POPULATIONS |
| 8.1 | Pregnancy |
| 8.2 | Lactation |
| 8.3 | Females and Males of Reproductive Potential |
| 8.4 | Pediatric Use |
| 8.5 | Geriatric Use |
| 8.6 | Hepatic Impairment |
| 11 | DESCRIPTION |
| 12 | CLINICAL PHARMACOLOGY |
| 12.1 | Mechanism of Action |
| 12.2 | Pharmacodynamics |
| 12.3 | Pharmacokinetics |
| 13 | NONCLINICAL TOXICOLOGY |
| 13.1 | Carcinogenesis, Mutagenesis, Impairment of Fertility |
| 13.2 | Animal Toxicology and/or Pharmacology |
| 14 | CLINICAL STUDIES |
| 14.1 | Previously Untreated ALK-Positive Metastatic NSCLC |
| 14.2 | Previously Treated ALK-Positive Metastatic NSCLC |
| 16 | HOW SUPPLIED/STORAGE AND HANDLING |
| 17 | PATIENT COUNSELING INFORMATION |

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZYKADIA[®] is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for treatment of metastatic NSCLC with ZYKADIA based on the presence of ALK positivity in tumor specimens [see *Indications and Usage (1), Clinical Studies (14.1)*].

Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at: <http://www.fda.gov/CompanionDiagnostics>.

2.2 Dosing and Administration

The recommended dose of ZYKADIA is 450 mg orally once daily with food until disease progression or unacceptable toxicity [see *Clinical Pharmacology (12.3)*].

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.

2.3 Dose Modifications for Adverse Reactions

Recommendations for dose modifications of ZYKADIA for adverse reactions are provided in Table 2.

Discontinue ZYKADIA for patients unable to tolerate 150 mg daily with food.

Table 1: ZYKADIA Dose Reductions

| Dose Reduction Schedule | Dose Level |
|-------------------------|--|
| Starting dose | 450 mg taken orally once daily with food |
| First dose reduction | 300 mg taken orally once daily with food |
| Second dose reduction | 150 mg taken orally once daily with food |

Table 2: ZYKADIA Dose Modifications for Adverse Reactions

| Adverse Reaction | ZYKADIA Dose Modification |
|---|---|
| Gastrointestinal Adverse Reactions | |
| 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. |
| Severe or intolerable nausea, vomiting or diarrhea despite optimal antiemetic or antidiarrheal therapy | Withhold until improved, then resume ZYKADIA with a 150 mg dose reduction. |
| Hyperglycemia | |
| Persistent hyperglycemia greater than 250 mg/dL despite optimal antihyperglycemic 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. |
| Pneumonitis | |
| Any Grade treatment-related ILD/pneumonitis | Permanently discontinue ZYKADIA. |
| Cardiac Arrhythmias | |
| 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 torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia | Permanently 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. |
| Hepatotoxicity | |
| ALT or AST elevation greater than 5 times ULN <u>with</u> 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 <u>with</u> total bilirubin elevation greater than 2 times ULN in the absence of cholestasis or hemolysis | Permanently discontinue ZYKADIA. |
| AST: aspartate aminotransferase; ALT: alanine aminotransferase; ULN: upper limit of normal; ILD: interstitial lung disease; ECG: electrocardiogram; bpm: beats per minute | |

2.4 Dose Modification for Strong CYP3A Inhibitors

Avoid concurrent use of strong CYP3A inhibitors during treatment with ZYKADIA [see *Drug Interactions (7.1), 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 CYP3A inhibitor.

2.5 Dose Modification for Patients with Severe Hepatic Impairment

For patients with severe hepatic impairment (Child-Pugh C), reduce the dose of ZYKADIA by approximately one-third, rounded to the nearest multiple of the 150 mg dosage strength [see *Use in Specific Populations (8.6), Clinical Pharmacology (12.3)*].

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

Data in the Warnings and Precautions section reflect the safety of ZYKADIA 750 mg daily under fasted conditions in 925 patients with ALK-positive NSCLC across a pool of seven clinical studies at systemic exposures similar to the recommended dose of 450 mg with food. In a dose optimization study (ASCEND-8), there were no clinically meaningful differences observed in the incidence of toxicities described in Warnings and Precautions between patients receiving 750 mg daily under fasted conditions and 450 mg with food, except for a reduction in gastrointestinal adverse reactions as described [see *Warnings and Precautions (5.1)*].

5.1 Gastrointestinal Adverse Reactions

Severe gastrointestinal toxicity occurred in patients treated with ZYKADIA 750 mg under fasted conditions. Diarrhea, nausea, vomiting, or abdominal pain occurred in 95% of 925 patients, including severe cases (Grade 3 or 4) in 14% of patients treated with ZYKADIA across clinical studies. Diarrhea, nausea, vomiting, or abdominal pain leading to dose interruptions or reductions occurred in 36% of patients and leading to treatment discontinuation occurred in 1.6% of patients.

The incidence and severity of gastrointestinal adverse reactions were reduced for patients treated with ZYKADIA 450 mg with food in a dose optimization study (ASCEND-8). Diarrhea, nausea, vomiting, or abdominal pain occurred in 76% of 89 patients treated with ZYKADIA at the recommended dose of 450 mg with food. Of these, the majority experienced Grade 1 events (51%). One patient experienced Grade 3 diarrhea. No patients had diarrhea, nausea, vomiting, or abdominal pain that required dose reduction; 8% of patients had diarrhea or nausea that required at least one dose interruption.

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 2 [see *Dosage and Administration (2.3), 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 28% and elevations in aspartate aminotransferase (AST) greater than 5 times ULN occurred in 16% of 925 patients across clinical studies. Concurrent elevations in ALT greater than 3 times the ULN and total bilirubin greater than 2 times the ULN, with alkaline phosphatase less than 2 times the ULN occurred in 0.3% of patients across clinical studies. Approximately 1.0% of patients required permanent discontinuation due to hepatotoxicity.

Monitor with liver laboratory tests including ALT, 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 2 [see *Dosage and Administration (2.3), Adverse Reactions (6)*].

5.3 Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, or fatal ILD/pneumonitis occurred in patients treated with ZYKADIA. Across clinical studies, ILD/pneumonitis was reported in 2.4% of 925 patients treated with ZYKADIA. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 3 or 4 ILD/pneumonitis was reported in 1.3% of patients, with fatal events reported in 0.2% of patients. Ten patients (1.1%) discontinued ZYKADIA across clinical studies 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 (2.3), Adverse Reactions (6)*].

5.4 QT Interval Prolongation

QTc interval prolongation, which may lead to an increased risk for ventricular tachyarrhythmia (e.g., torsades de pointes) or sudden death, occurred in patients treated with ZYKADIA. Across clinical studies, 6% of 919 patients with at least one post-baseline ECG assessment experienced a QTc interval increase over baseline of greater than 60 msec. Approximately 1.3% of patients taking ZYKADIA 750 mg fasted were found to have a QTc greater than 500 msec. A pharmacokinetic/pharmacodynamic analysis suggested that ZYKADIA causes concentration-dependent increases in the QTc interval. Across clinical studies, 0.2% of patients discontinued ceritinib due to QTc prolongation.

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 2. Permanently discontinue ZYKADIA in patients who develop QTc interval prolongation in combination with torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia [see *Dosage and Administration (2.3), Clinical Pharmacology (12.2)*].

5.5 Hyperglycemia

Hyperglycemia occurred in patients receiving ZYKADIA. Across clinical studies, CTCAE Grade 3 or 4 hyperglycemia, based on laboratory values, occurred in 13% of 925 patients. 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 2. If adequate hyperglycemic control cannot be achieved with optimal medical management, permanently discontinue ZYKADIA [see *Dosage and Administration (2.3), Adverse Reactions (6)*].

5.6 Bradycardia

Bradycardia occurred in patients receiving ZYKADIA. Across clinical studies, sinus bradycardia, defined as a heart rate of less than 50 beats per minute (bpm), was noted as a new finding in 1% of 925 patients. Bradycardia was reported as an adverse drug reaction in 1% of patients. No patient required discontinuation and 0.1% required interruption with subsequent dose reduction for bradycardia.

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 2, upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring [see *Dosage and Administration (2.3), Adverse Reactions (6)*].

5.7 Pancreatitis

Pancreatitis occurred in patients receiving ZYKADIA. Pancreatitis, including one fatality, occurred in less than 1% of patients receiving ZYKADIA in clinical studies. CTCAE Grade 3 or 4 elevations of amylase occurred in 7% of patients receiving ZYKADIA across clinical studies, while CTCAE Grade 3 or 4 elevations of lipase occurred in 14% of patients. 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 2 [*see Dosage and Administration (2.3), Adverse Reactions (6)*].

5.8 Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animal studies, ZYKADIA can 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. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYKADIA and for 6 months following completion of therapy. Based on the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with ZYKADIA and for 3 months following completion of therapy [*see Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)*].

6 ADVERSE REACTIONS

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

- Gastrointestinal Adverse Reactions [*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), 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 data in the Warnings and Precautions section reflect exposure to ZYKADIA 750 mg once daily under fasted conditions in 925 patients with ALK-positive NSCLC across seven clinical studies, including ASCEND-4 and ASCEND-1, described below, a randomized active-controlled study, two single arm studies, and two dose-escalation studies. The majority of patients enrolled in these studies had received prior treatment with chemotherapy and/or crizotinib for NSCLC. Among these 925 patients the most common adverse reactions (greater than or equal to 25% incidence) were diarrhea, nausea, fatigue, vomiting, abdominal pain, decreased appetite, and weight loss. Approximately 45% of patients initiating treatment with ZYKADIA 750 mg under fasted conditions had an adverse reaction that required at least one dose reduction and 66% of patients had an adverse reaction that required at least one dose interruption. The median time to first dose reduction due to any reason was 7 weeks.

In ASCEND-8, a dose optimization study, ZYKADIA 450 mg daily with food (N = 89) was compared to 750 mg daily under fasted conditions (N = 90) in both previously treated and untreated patients with ALK-positive NSCLC. The overall safety profile of ZYKADIA 450 mg with food was consistent with ZYKADIA 750 mg fasted, except for a reduction in gastrointestinal adverse reactions, while achieving comparable steady-state exposure [*see Clinical Pharmacology (12.3)*]. The incidence and severity of gastrointestinal adverse reactions (diarrhea 56%, nausea 45%, vomiting 35%) were reduced for patients treated with ZYKADIA 450 mg with food; the only Grade ≥ 3 adverse reaction was Grade 3 diarrhea in one patient (1.1%) [*see Warnings and Precautions (5.1)*]. In patients treated with ZYKADIA 450 mg with food, 10% of patients had an adverse reaction that required at least one dose reduction and 42% of patients had an adverse reaction that required at least one dose interruption. The median time to first dose reduction due to any reason was 8 weeks.

Previously Untreated ALK-Positive Metastatic NSCLC

The safety evaluation of ZYKADIA is based on ASCEND-4, an open-label, randomized, active-controlled multicenter study of 376 previously untreated ALK-positive NSCLC patients. Patients received ZYKADIA 750 mg daily (N = 189) under fasted conditions or chemotherapy plus maintenance chemotherapy (N = 187). Chemotherapy regimens were pemetrexed (500 mg/m²) plus investigator's choice of cisplatin (75 mg/m²) or carboplatin [area under the curve (AUC) of 5 - 6 mg*min/mL] administered every 21 days. Patients who completed 4 cycles of chemotherapy without progressive disease received pemetrexed (500 mg/m²) as single-agent maintenance therapy every 21 days.

The demographic characteristics of the study population were 57% female, median age 54 years (range: 22 to 81 years), 22% age 65 years or older, 54% White, 42% Asian, 2% Black, and 2% other races. Patients were enrolled in Europe (53%), Asia Pacific (42%), and South America (5%) regions. The majority of patients had adenocarcinoma (97%), never smoked (61%), and 32% had brain metastases at screening. The median duration of exposure to ZYKADIA was 18 months.

Serious adverse reactions were reported in 72 patients (38%) treated with ZYKADIA. The most frequent serious adverse reactions were pneumonia (4%), pleural effusion (4%), vomiting (4%), nausea (3%), dyspnea (3%), hyperglycemia (3%), AST increased (2%), lung infection (2%), and pericardial effusion (2%). Among patients treated with ZYKADIA, dose interruptions due to adverse reactions occurred in 77%, dose reductions were required in 66%, and adverse reactions that led to discontinuation of therapy occurred in 12% of patients. The most frequent adverse reactions, reported in at least 10% of patients treated with ZYKADIA, that led to dose interruptions or reductions were: ALT increased (48%), AST increased (34%), vomiting (15%), blood creatinine increased (14%), GGT increased (13%), diarrhea (13%), and nausea (13%). The most frequent adverse reactions that led to discontinuation of ZYKADIA in 1% or more of patients in ASCEND-4 were blood creatinine increased (2.1%), amylase increased (1.1%), and lipase increased (1.1%). The following fatal adverse reactions occurred in 4 patients treated with ZYKADIA: myocardial infarction, respiratory tract infection, pneumonitis, and unknown cause.

Tables 3 and 4 summarize adverse reactions and laboratory abnormalities, respectively, in ASCEND-4.

Table 3: Adverse Reactions (> 10% for All NCI CTCAE* Grades or ≥ 2% for Grades 3-4) of Patients in ASCEND-4

| | ZYKADIA N = 189 | | Chemotherapy N = 175 ^a | |
|----------------------------------|--------------------|-----------|--------------------------------------|-----------|
| | All Grades | Grade 3-4 | All Grades | Grade 3-4 |
| | % | % | % | % |
| Gastrointestinal** | | | | |
| Diarrhea | 85 | 4.8 | 11 | 1.1 |
| Nausea | 69 | 2.6 | 55 | 5 |
| Vomiting | 67 | 5 | 36 | 6 |
| Abdominal pain ^b | 40 | 3.7 | 13 | 0 |
| Constipation | 20 | 0 | 22 | 0 |
| Esophageal disorder ^c | 15 | 0.5 | 8 | 0.6 |
| General | | | | |
| Fatigue ^d | 45 | 7 | 49 | 6 |
| Non-cardiac chest pain | 21 | 1.1 | 10 | 0.6 |
| Back pain | 19 | 1.6 | 18 | 2.3 |
| Pain in extremity | 13 | 0 | 7 | 0 |
| Musculoskeletal pain | 11 | 0.5 | 6 | 0.6 |
| Pruritus | 11 | 0.5 | 5 | 0 |
| Pyrexia | 19 | 0 | 14 | 1.1 |
| Metabolism And Nutrition | | | | |
| Decreased appetite | 34 | 1.1 | 32 | 1.1 |
| Weight loss | 24 | 3.7 | 15 | 0.6 |
| Respiratory | | | | |
| Cough | 25 | 0 | 17 | 0 |
| Neurologic | | | | |
| Headache | 19 | 0.5 | 13 | 1.1 |
| Dizziness | 12 | 1.1 | 10 | 0.6 |
| Skin | | | | |
| Rash ^e | 21 | 1.1 | 8 | 0.6 |
| Cardiac | | | | |
| Prolonged QT interval | 12 | 2.6 | 1.1 | 0.6 |
| Pericarditis ^f | 4.2 | 1.6 | 2.3 | 1.1 |

*National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03)

**For frequency of gastrointestinal adverse reactions at the recommended dose of 450 mg with food, see *Gastrointestinal Adverse Reactions (5.1) and Clinical Trials Experience (6.1)*.

^aTwelve patients randomized to chemotherapy did not receive study drug.

^bAbdominal pain (abdominal pain, abdominal pain upper, abdominal discomfort, epigastric discomfort)

^cEsophageal disorder (dyspepsia, gastroesophageal reflux disease, dysphagia)

^dFatigue (fatigue and asthenia)

^eRash (rash, dermatitis acneiform, rash maculo-papular)

^fPericarditis (pericardial effusion and pericarditis)

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ZYKADIA 750 mg fasted included: vision disorder (4%; comprised of vision impairment, blurred vision, photopsia, accommodation disorder,

presbyopia, reduced visual acuity, or vitreous floaters), bradycardia (4%), ILD/pneumonitis (2%), hepatotoxicity (2%) and renal failure (2%).

Table 4: Laboratory Abnormalities Occurring in > 10% (All NCI CTCAE Grades) of Patients in ASCEND-4

| | ZYKADIA N = 189 | | Chemotherapy N = 175 ^a | |
|---|--------------------|-----------|--------------------------------------|-----------|
| | All Grades | Grade 3–4 | All Grades | Grade 3–4 |
| | % | % | % | % |
| Hematology | | | | |
| Anemia | 67 | 4.2 | 84 | 11 |
| Neutropenia | 27 | 2.1 | 58 | 20 |
| Thrombocytopenia | 16 | 1.0 | 38 | 4.6 |
| Chemistry | | | | |
| Increased ALT | 91 | 34 | 65 | 3.4 |
| Increased AST | 86 | 21 | 58 | 2.3 |
| Increased gamma-glutamyl transpeptidase (GGT) | 84 | 49 | 67 | 10 |
| Increased alkaline phosphatase | 81 | 12 | 47 | 1.7 |
| Increased creatinine | 77 | 4.2 | 37 | 0.6 |
| Hyperglycemia | 53 | 10 | 67 | 10 |
| Increased amylase | 37 | 8 | 43 | 4.5 |
| Decreased phosphate | 38 | 3.7 | 27 | 4.0 |
| Increased bilirubin (total) | 15 | 0.5 | 6 | 0.6 |
| Increased lipase ^b | 13 | 6 | 7 | 0.6 |

^aTwelve patients randomized to chemotherapy did not receive study drug.
^bIn the ZYKADIA arm, no patients had baseline lipase laboratory assessments, 112 had post-baseline assessments. In the chemotherapy arm, one patient had baseline lipase laboratory assessments but no post-baseline assessment; 49 patients had post-baseline assessments.

Previously Treated ALK-Positive Metastatic NSCLC

The safety evaluation of ZYKADIA is based on 255 ALK-positive patients in ASCEND-1 (246 patients with NSCLC and 9 patients with other cancers who received ZYKADIA at a dose of 750 mg daily under fasted conditions). 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 metastases (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 ASCEND-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 ASCEND-1 were pneumonia, ILD/pneumonitis, and decreased appetite.

Tables 5 and 6 summarize the common adverse reactions and laboratory abnormalities observed in ZYKADIA-treated patients.

Table 5: Adverse Reactions (> 10% for All NCI CTCAE* Grades or ≥ 2% for Grades 3-4) in ALK-Positive Patients Treated with ZYKADIA in ASCEND-1

| | ZYKADIA N = 255 | |
|--|--------------------|-----------|
| | All Grades | Grade 3-4 |
| | % | % |
| Gastrointestinal** | | |
| Diarrhea | 86 | 6 |
| Nausea | 80 | 4 |
| Vomiting | 60 | 4 |
| Abdominal pain ^a | 54 | 2 |
| Constipation | 29 | 0 |
| Esophageal disorder ^b | 16 | 1 |
| General | | |
| Fatigue ^c | 52 | 5 |
| Metabolism and Nutrition | | |
| Decreased appetite | 34 | 1 |
| Skin | | |
| Rash ^d | 16 | 0 |
| Respiratory | | |
| Interstitial lung disease/pneumonitis | 4 | 3 |
| <p>*National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03) **For frequency of gastrointestinal adverse reactions at the recommended dose of 450 mg with food, see <i>Gastrointestinal Adverse Reactions (5.1) and Clinical Trials Experience (6.1)</i>. ^aAbdominal pain (abdominal pain, upper abdominal pain, abdominal discomfort, epigastric discomfort) ^bEsophageal disorder (dyspepsia, gastroesophageal reflux disease, dysphagia) ^cFatigue (fatigue, asthenia) ^dRash (rash, maculopapular rash, acneiform dermatitis)</p> | | |

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ZYKADIA 750 mg fasted 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 6: Key Laboratory Abnormalities Occurring in > 10% (All NCI CTCAE Grades) of ALK-Positive Patients Treated with ZYKADIA in ASCEND-1

| | ZYKADIA N = 255 | |
|-----------------------------|--------------------|-----------|
| | All Grades | Grade 3-4 |
| | % | % |
| Hematology | | |
| Anemia | 84 | 5 |
| Chemistry | | |
| Increased ALT | 80 | 27 |
| Increased AST | 75 | 13 |
| Increased creatinine | 58 | 2 |
| Hyperglycemia | 49 | 13 |
| Decreased phosphate | 36 | 7 |
| Increased lipase | 28 | 10 |
| Increased bilirubin (total) | 15 | 1 |

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Ceritinib

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 CYP3A 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

CYP3A Substrates

Ceritinib increased the systemic exposure of a sensitive CYP3A substrate (midazolam) [see *Clinical Pharmacology (12.3)*]. Avoid coadministration of ZYKADIA with sensitive CYP3A substrates. If concomitant use is unavoidable, consider dose reduction of the sensitive CYP3A substrate(s). If ZYKADIA is coadministered with other CYP3A substrates, refer to the CYP3A substrate labeling for dosage recommendation with strong CYP3A inhibitors.

CYP2C9 Substrates

Ceritinib increased the systemic exposure of a CYP2C9 substrate (warfarin) [see *Clinical Pharmacology (12.3)*]. Increase the frequency of INR monitoring if coadministration with warfarin is unavoidable as the anti-coagulant effect of warfarin may be enhanced.

Avoid coadministration of ZYKADIA with CYP2C9 substrates for which minimal concentration changes may lead to serious toxicities. If concomitant use of such CYP2C9 substrates is unavoidable, consider dose reduction for the coadministered CYP2C9 substrates.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal studies and its mechanism of action, ZYKADIA can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. The limited available data on the use of ZYKADIA in pregnant women are insufficient to inform a risk. Administration of ceritinib to rats and rabbits during the period of organogenesis at maternal plasma exposures below the recommended human dose caused increases in skeletal anomalies in rats and rabbits (see *Data*). Advise a pregnant woman of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.

Data

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, embryoletality was observed in rabbits at a dose of 50 mg/kg.

8.2 Lactation

Risk Summary

There are no data regarding the presence of ceritinib or its metabolites in human milk, the effects of ceritinib on the breastfed infant, or its effects on milk production. Because of the potential for serious adverse reactions including gastrointestinal adverse reactions, hepatotoxicity, pneumonitis, bradycardia and pancreatitis, advise a woman not to breastfeed during treatment with ZYKADIA and for 2 weeks following completion of therapy.

8.3 Females and Males of Reproductive Potential

Contraception

Females

ZYKADIA can 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 6 months following completion of therapy.

Males

Based on the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with ZYKADIA and for 3 months following completion of therapy [see *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 925 patients in clinical studies of ZYKADIA, 18% were 65 years or older, while 5% were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

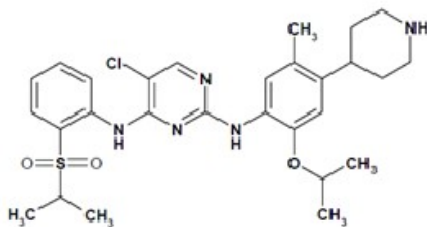
8.6 Hepatic Impairment

For patients with severe hepatic impairment (Child-Pugh C), reduce the dose of ZYKADIA by approximately one-third, rounded to the nearest multiple of the 150 mg dosage strength [see *Dosage and Administration (2.5), Clinical Pharmacology (12.3)*]. No dose adjustment is recommended in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

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/mol. 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.

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, indigotine, 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 925 patients treated with ZYKADIA 750 mg once daily under fasted conditions. Twelve of 925 patients (1.3%) were found to have a QTc greater than 500 msec and 58 patients (6%) had an increase from baseline QTc greater than 60 msec. In ASCEND-4, 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 15.3 msec at ZYKADIA 750 mg once daily under fasted conditions. A pharmacokinetic/pharmacodynamic analysis suggested concentration-dependent QTc interval prolongation [see *Warnings and Precautions (5.4)*].

Based on central review of ECG data, 10 of 925 patients (1.1%) had bradycardia defined as less than 50 bpm.

12.3 Pharmacokinetics

Absorption

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

Following ZYKADIA 750 mg once daily dosing under fasted conditions, 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 under fasted conditions.

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.

In a dose optimization study (ASCEND-8) in patients receiving ZYKADIA 450 mg or 600 mg daily with food (approximately 100 to 500 calories and 1.5 to 15 grams of fat) or 750 mg daily under fasted conditions, there was no clinically meaningful difference in the systemic steady-state exposure of ceritinib (AUC) for the 450 mg with food arm ($n = 36$) compared to the 750 mg fasted arm ($n = 31$). The steady-state AUC increased by 24% and C_{\max} increased by 25% in the 600 mg with food arm ($n = 30$) compared to the 750 mg fasted arm ($n = 31$).

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 fasted 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 fasted 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 under fasted conditions, 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 under fasted conditions, 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: Following a single 750 mg ZYKADIA dose under fasted conditions, the geometric mean systemic exposure (AUC_{inf}) of ceritinib was increased by 66% and unbound ceritinib AUC_{inf} was increased by 108% in subjects with severe (Child-Pugh C) hepatic impairment compared to healthy subjects with normal hepatic function [see *Dosage and Administration* (2.5), *Use in Specific Populations* (8.6)]. Total and unbound systemic exposure of ceritinib were similar in subjects with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment compared to healthy subjects with normal hepatic function.

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). Ceritinib exposures were similar between patients with mild-to-moderate renal impairment and patients with normal renal function based on a population pharmacokinetic analysis of 345 patients with mild renal impairment (CL_{cr} 60 to less than 90 mL/min), 82 patients with moderate renal impairment (CL_{cr} 30 to less than 60 mL/min) and 546 patients with normal renal function (greater than or equal to 90 mL/min). Patients with severe renal impairment (CL_{cr} 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 fasted ZYKADIA dose with ketoconazole (a strong CYP3A inhibitor) 200 mg twice daily for 14 days increased ceritinib AUC by 2.9-fold and C_{max} by 22% 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 (2.4)*].

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

Effect of Ceritinib on CYP3A Substrates: Coadministration of a single dose of midazolam (a sensitive CYP3A substrate) following 3 weeks of ZYKADIA (750 mg daily under fasted conditions) increased the midazolam AUC by 5.4-fold and C_{max} by 1.8-fold compared to midazolam administered alone [see *Drug Interactions (7.2)*].

Effect of Ceritinib on CYP2C9 Substrates: Coadministration of a single dose of warfarin (a CYP2C9 substrate) following 3 weeks of ZYKADIA (750 mg daily under fasted conditions) increased the S-warfarin AUC by 54% with no change in C_{max} compared to warfarin administered alone [see *Drug Interactions (7.2)*].

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 under fasted conditions with a proton pump inhibitor (esomeprazole) 40 mg daily for 6 days in healthy subjects decreased ceritinib AUC by 76% and C_{max} by 79%. However, coadministration of a single 750 mg ZYKADIA dose under fasted conditions with proton pump inhibitors for 6 days in a subgroup of patients from ASCEND-1 suggested less effect on ceritinib exposure than that observed in healthy subjects as AUC decreased by 30% and C_{max} decreased by 25% 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.

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

14.1 Previously Untreated ALK-Positive Metastatic NSCLC

The efficacy of ZYKADIA for the treatment of patients with ALK-positive NSCLC who had not received prior systemic therapy for metastatic disease was established in an open-label, randomized, active-controlled, multicenter study (ASCEND-4, NCT01828099). Patients were required to have WHO performance status 0-2 and ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx Assay. Neurologically stable patients with central nervous system (CNS) metastases that did not require increasing doses of steroids to manage CNS symptoms were permitted to enroll. Patients with uncontrolled diabetes mellitus; a history of interstitial lung disease or interstitial pneumonitis; or a history of pancreatitis or increased amylase or lipase that was due to pancreatic disease were not eligible.

The major efficacy outcome measure was progression-free survival (PFS) as determined by blinded independent review committee (BIRC) according to RECIST v1.1. Additional efficacy outcome measures were overall survival (OS), overall response rate (ORR) and duration of response (DOR) determined by BIRC, overall intracranial response rate (OIRR), duration of intracranial response (DOIR) determined by BIRC neuro-radiologist, and patient reported outcomes.

Patients were randomized 1:1 to receive ZYKADIA 750 mg orally daily under fasted conditions or chemotherapy plus maintenance chemotherapy. Randomization was stratified by World Health Organization (WHO) performance status, prior adjuvant/neoadjuvant chemotherapy and presence or absence of brain metastases. Patients randomized to chemotherapy received pemetrexed (500 mg/m²) and investigator's choice of cisplatin (75 mg/m²) or carboplatin (AUC of 5 - 6 mg*min/mL) administered on day 1 of each 21-day cycle for a maximum of 4 cycles followed by pemetrexed (500 mg/m²) every 21 days. Treatment in both arms was continued until disease progression or unacceptable toxicity.

A total of 376 patients were randomized to receive ZYKADIA (n = 189) or chemotherapy (n = 187). The demographic characteristics of the study population were 57% female, median age 54 years (range: 22 to 81 years), 22% age 65 years or older, 54% White, 42% Asian, 2% Black, and 2% other races. The majority of patients had adenocarcinoma (97%) and never smoked (61%). CNS metastases were present in 32% (n = 121) of patients. Approximately half (n = 55) had measurable CNS metastases as determined by BIRC neuro-radiologist and 71% (n = 39) of these patients received no prior intracranial radiotherapy. Of those randomized to chemotherapy, 43% received ZYKADIA as the next antineoplastic therapy after platinum-based chemotherapy.

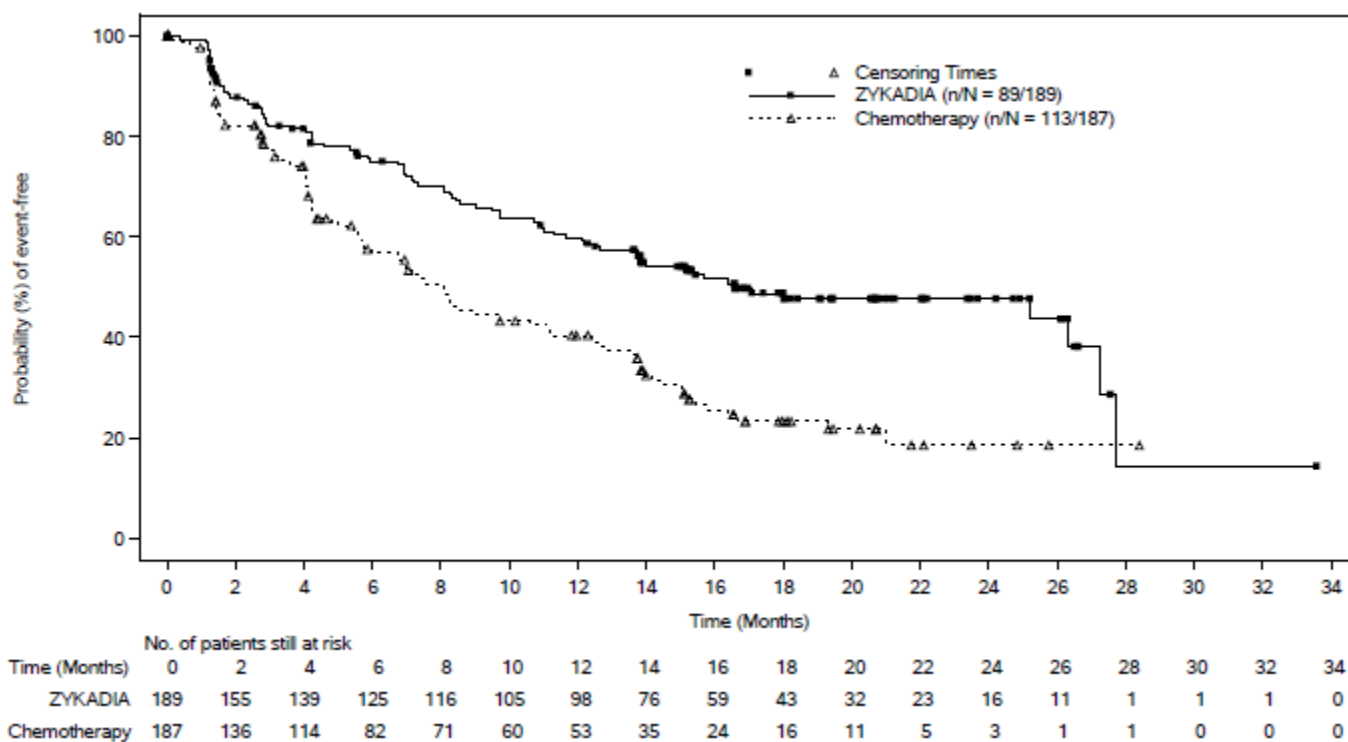
Efficacy results from ASCEND-4 are summarized in Table 7 and Figure 1.

Table 7: Efficacy Results by BIRC Assessment in ASCEND-4

| | ZYKADIA (N = 189) | Chemotherapy (N = 187) |
|--|------------------------------|-----------------------------------|
| Progression-Free Survival | | |
| Number of events, n (%) | 89 (47%) | 113 (60%) |
| Progressive disease, n (%) | 79 (42%) | 105 (56%) |
| Death, n (%) | 10 (5%) | 8 (4%) |
| Median PFS in months (95% CI) | 16.6 (12.6, 27.2) | 8.1 (5.8, 11.1) |
| Hazard ratio (95% CI) ^a | 0.55 (0.42, 0.73) | |
| P-value ^b | < 0.0001 | |
| Overall Response Rate | | |
| Overall response rate, % (95% CI) ^c | 73 (66, 79) | 27 (21, 34) |
| Complete response, % | 1 | 0 |
| Partial response, % | 72 | 27 |
| Duration of response | | |
| Number of responders | n = 137 | n = 50 |
| Median in months (95% CI) | 23.9 (16.6, NE) | 11.1 (7.8, 16.4) |
| BIRC: Blinded Independent Review Committee; CI: Confidence Interval; NE: Not Estimable | | |
| ^a Cox proportional hazards model stratified by brain metastases (absence vs. presence), WHO performance status (0 vs. ≥ 1), and prior adjuvant chemotherapy (absence vs. presence). | | |
| ^b Log-rank test stratified by brain metastases (absence vs. presence), WHO performance status (0 vs. ≥ 1), and prior adjuvant chemotherapy (absence vs. presence). | | |
| ^c Clopper and Pearson exact binomial 95% confidence interval. | | |

There was no significant difference in OS in a pre-specified interim analysis conducted at 42% of the events required for the final analysis.

Figure 1: Kaplan-Meier Plot of Progression-Free Survival as Assessed by BIRC by Treatment Arm in ASCEND-4



Antitumor activity of ZYKADIA in the brain was assessed in patients with measurable disease as determined by the BIRC neuro-radiologist at baseline (N = 55) according to RECIST 1.1.

Table 8: BIRC Assessed CNS Responses in Patients with Measurable CNS Lesions in ASCEND-4

| | ZYKADIA | Chemotherapy |
|---|----------------|--------------|
| Intracranial Tumor Response Assessment | N = 28 | N = 27 |
| Overall intracranial response rate, % (95% CI) ^a | 57% (37, 76) | 22% (9, 42) |
| Complete response, % | 7% | 7% |
| Partial response, % | 50% | 15% |
| Duration of Intracranial Response | | |
| Number of responders | n = 16 | n = 6 |
| Median in months (95% CI) | 16.6 (8.1, NE) | NE (1.5, NE) |
| BIRC: Blinded Independent Review Committee; CI: Confidence Interval; NE: Not Estimable | | |
| ^a Clopper and Pearson exact binomial 95% confidence interval | | |

Exploratory analyses of patient-reported outcome measures suggested a delay in time to development of or worsening of shortness of breath in patients treated with ZYKADIA as compared to chemotherapy. The patient-reported delay in onset or worsening of shortness of breath may be an overestimation, because patients were not blinded to treatment assignment.

14.2 Previously Treated ALK-Positive Metastatic NSCLC

The efficacy of ZYKADIA was established in a multicenter, single-arm, open-label clinical trial (ASCEND-1, NCT01283516). 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 under fasted conditions. The major efficacy outcome measure was objective response rate (ORR) according to RECIST v1.0 as evaluated by both investigators and a Blinded Independent 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 metastases 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 ASCEND-1 are summarized in Table 9.

Table 9: Overall Response Rate and Duration of Response¹ in ASCEND-1

| Efficacy Parameter | Investigator Assessment (N = 163) | BIRC Assessment (N = 163) |
|---|--|--------------------------------------|
| Overall Response Rate (95% CI) | 54.6% (47, 62) | 43.6% (36, 52) |
| Complete response, % | 1.2% | 2.5% |
| Partial response, % | 53.4% | 41.1% |
| Duration of Response, median (months) (95% CI) | 7.4 (5.4, 10.1) | 7.1 (5.6, NE) |
| BIRC: Blinded Independent Review Committee; NE: Not Estimable | | |
| ¹ Overall Response Rate and Duration of Response determined by RECIST v1.0 | | |

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).

Gastrointestinal Adverse Reactions

Inform patients that diarrhea, nausea, vomiting, and abdominal pain are the most commonly reported gastrointestinal adverse reactions in patients treated with ZYKADIA. Inform patients of supportive care options such as antiemetic and antidiarrheal medications. Advise patients to contact their healthcare provider for severe or intolerable 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)].

Hepatotoxicity

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)].

Interstitial Lung Disease (ILD)/Pneumonitis

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)].

Arrhythmias

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)].

Hyperglycemia

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)].

Pancreatitis

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)*].

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [*see Warnings and Precautions (5.8), Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)*].

Advise females of reproductive potential to use effective contraception during treatment with ZYKADIA and for 6 months following completion of therapy [*see Warnings and Precautions (5.8), Use in Specific Populations (8.1, 8.3)*]. Advise males with female partners of reproductive potential to use condoms during treatment with ZYKADIA and for 3 months following completion of therapy [*see Warnings and Precautions (5.8), Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)*].

Lactation

Advise females not to breastfeed during treatment with ZYKADIA and for 2 weeks following completion of therapy [*see Use in Specific Populations (8.2)*].

Drug Interactions

Inform patients not to consume grapefruit and grapefruit juice during treatment with ZYKADIA [*see Drug Interactions (7.1)*].

Dosing Instructions

Advise patients to take ZYKADIA with food [*see Dosage and Administration (2.2)*]. Advise patients to make up a missed dose of ZYKADIA unless the next dose is due within 12 hours [*see Dosage and Administration (2.2)*].

Distributed by:

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

© Novartis

T201X-XX

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 may cause stomach and intestinal problems, including diarrhea, nausea, vomiting, and stomach-area pain. Follow your healthcare provider's instructions about taking medicines to help with these symptoms. Call your healthcare provider for advice if your symptoms are severe or cannot be tolerated.

Liver problems. ZYKADIA may cause liver injury. Your healthcare provider should do blood tests at least every month to check your liver during treatment with 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

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

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 can 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 6 months after stopping ZYKADIA. Talk to your healthcare provider about birth control methods that may be right for you. Tell your healthcare provider right away if you become pregnant or think that you may be pregnant.
 - Males with female partners who are able to become pregnant should use condoms during treatment with ZYKADIA and for 3 months after stopping ZYKADIA.
- are breastfeeding or plan to breastfeed. It is not known if ZYKADIA passes into your breast milk. Do not breastfeed during treatment with ZYKADIA and for 2 weeks after stopping 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 ZYKADIA unless your healthcare provider tells you to.
- Take ZYKADIA one time a day.
- Take ZYKADIA with food.
- If you vomit after taking ZYKADIA, do not take an additional dose. 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 weight loss

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 that is written for health professionals.

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, indigotine, and titanium dioxide

Distributed by: Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936. For more information, go to www.US.ZYKADIA.com or call 1-888-669-6682.

T2017-124