PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrZYKADIA®

Ceritinib Capsules

Capsules, 150 mg, Oral

Protein Kinase Inhibitor (L01XE)

ZYKADIA (ceritinib) as monotherapy, indicated for:

- the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) who have progressed on or who were intolerant to crizotinib,

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for ZYKADIA please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html.

ZYKADIA as monotherapy, indicated for:

- the first-line treatment of adult patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC,

has been issued market authorization without conditions.

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What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dose Adjustment	02/2022
7 WARNINGS AND PRECAUTIONS, Gastrointestinal	02/2022

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ZYKADIA® (ceritinib) as monotherapy is indicated for:

- the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC)
- **NOC/c:** the treatment of adult patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC who have progressed on or who were intolerant to crizotinib

Marketing authorization with conditions was based on a primary efficacy endpoint of overall response rate (ORR) as well as duration of response (DOR) in clinical Study X2101, based on investigator assessment using RECIST (see 14 CLINICAL TRIALS).

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of ZYKADIA have not been established in pediatric patients.

1.2 Geriatrics

Geriatrics (≥65 years of age): Across seven clinical studies in patients with ALK+ advanced NSCLC receiving a fasted dose of 750 mg daily, 168 of 925 patients (18.2%) treated with ZYKADIA were aged 65 years and older. No overall differences in safety or efficacy were observed between younger (<65 years) and older patients (≥ 65 years).

2 CONTRAINDICATIONS

Patients with a known hypersensitivity to the active substance, ceritinib, or to any ingredient in the formulation. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, and COMPOSITION AND PACKAGING.

Patients with congenital long QT syndrome or with a persistent Fridericia-corrected electrocardiogram interval (QTcF) of >500 msec (see 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- QT interval prolongation. (See 3 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS, 9 DRUG INTERACTIONS)
- Interstitial Lung Disease/Pneumonitis, including fatal cases. (See 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS)
- ZYKADIA has not been studied in patients with severe renal impairment requiring peritoneal dialysis or hemodialysis. (See 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS)
- Hepatotoxicity. (See 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS)
- Gastrointestinal toxicity. (See 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS)

ZYKADIA (ceritinib) should only be prescribed and supervised by a qualified physician experienced in the use of anticancer agents.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Renal impairment

Ceritinib has not been evaluated in patients with renal impairment in a dedicated study. However, based upon available data, ceritinib elimination via the kidney is negligible. Dose adjustment is not required for patients with mild and moderate renal impairment based on results of a population pharmacokinetic analysis. Caution should be used in patients with severe renal impairment as there is no experience with ceritinib in this population (see 10 CLINICAL PHARMACOLOGY).

- 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 7 WARNINGS AND PRECAUTIONS, 7.1 Special populations and 10 CLINICAL PHARMACOLOGY).

4.2 Recommended Dose and Dosage Adjustment

- Recommended Dose

The recommended dose of ZYKADIA is 450 mg taken orally once daily with food at the same time each day. Food can range from a snack to a full meal (see 9 DRUG INTERACTIONS and 10 CLINICAL PHARMACOLOGY).

The maximum recommended dose is 450 mg taken orally once daily with food.

Treatment should be continued as long as the patient is deriving clinical benefit from therapy.

- Dosage Adjustments

Temporary dose interruption and/or dose reduction of ZYKADIA therapy may be required based on individual safety and tolerability. If dose reduction is required due to any adverse drug reaction, then the daily dose of ZYKADIA should be reduced by decrements of 150 mg.

Early identification and management of adverse drug reactions (including gastrointestinal disorders) with standard supportive care measures should be considered.

Discontinue ZYKADIA in patients unable to tolerate 150 mg taken once daily with food.

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

Table 1 ZYKADIA dose adjustment and management recommendations for adverse drug reactions

Criteria	ZYKADIA Dosing
Severe or intolerable nausea, vomiting, or diarrhea despite optimal anti-emetic or anti-diarrheal therapy	Withhold ZYKADIA until improved, then reinitiate ZYKADIA by reducing dose by 150 mg

Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation greater than 5 times upper limit of normal (ULN) with concurrent total bilirubin less than or equal to 1.5 times ULN	Withhold ZYKADIA until recovery to baseline ALT/AST levels or to less than or equal to 3 times ULN, then reinitiate ZYKADIA by reducing dose by one 150 mg
ALT or AST elevation greater than 3 times ULN with concurrent 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 greater than 500 msec on at least 2 separate electrocardiograms (ECGs)	Withhold ZYKADIA until recovery to baseline or to a QTc less than 481 msec, then reinitiate ZYKADIA by reducing dose by 150 mg
Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue ZYKADIA
Symptomatic bradycardia that is not life-threatening in patients who are taking a concomitant medication also known to cause bradycardia or hypotension.[a]	Withhold ZYKADIA until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, reinitiate ZYKADIA at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above
Symptomatic bradycardia that is not life-threatening in patients who are not taking a concomitant medication also known to cause bradycardia or hypotension [a]	Withhold ZYKADIA until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, reinitiate ZYKADIA by reducing dose by 150 mg upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above
Bradycardia[a] (that is life-threatening or requires medical intervention) in patients taking a concomitant medication also known to cause bradycardia or hypotension.	Withhold ZYKADIA until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, reinitiate ZYKADIA by reducing the dose by 150mg, with frequent monitoring[b]
Bradycardia[a] (that is life-threatening or requires urgent intervention) in patients who are not taking a concomitant	Permanently discontinue ZYKADIA

medication also known to cause bradycardia or hypotension	
Severe (grade 3) or intolerable nausea, vomiting or diarrhea despite optimal anti-emetic or anti-diarrheal therapy	Withhold ZYKADIA until improved, then reinitiate ZYKADIA by reducing dose by 150 mg
Persistent hyperglycemia greater than 250mg/dL despite optimal anti-hyperglycemic therapy	Withhold ZYKADIA until hyperglycemia is adequately controlled, then reinitiate ZYKADIA by reducing dose by 150 mg If adequate glucose control cannot be achieved with optimal medical management, permanently discontinue ZYKADIA
Elevated lipase or amylase greater than or equal to grade 3 (greater than 2 times ULN)	Withhold ZYKADIA until lipase or amylase returns to less than or equal to grade 1 (less than 1.5 times ULN), then reinitiate by reducing dose by 150 mg
[a] Heart rate less than 60 beats per minute (bpm) [b] Permanently discontinue for recurrence	

4.3 Administration

ZYKADIA should be administered orally once daily at the same time every day. ZYKADIA capsules should be swallowed whole with water. The capsules should not be chewed or crushed. (see 10 CLINICAL PHARMACOLOGY).

4.4 Missed Dose

If a dose is missed, the patient should make up that dose, unless the next dose is due within 12 hours. If vomiting occurs during the course of treatment, the patient should not take an additional dose, but should continue with the next scheduled dose.

5 OVERDOSAGE

A 750 mg once daily fasted dosing regimen was the maximum tolerated dose for ZYKADIA determined in a Phase I dose-escalation study in patients with ALK-positive malignancies. There is limited reported experience with overdose in humans. General supportive measures, including ECG monitoring, should be initiated in all cases of overdose.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	capsule 150 mg	Capsule content: colloidal anhydrous silica; hydroxypropyl cellulose low-substituted; magnesium stearate; microcrystalline cellulose; sodium starch glycolate. The capsule shell components contain gelatin; indigotine (E132); titanium dioxide (E171). The printing ink contains black iron oxide.

Dosage Form

ZYKADIA (ceritinib) 150 mg capsules: Hard gelatin capsule, size #00, opaque white and opaque blue capsule, opaque blue cap marked in black ink with “LDK 150MG”, opaque white body marked in black ink with “NVR”.

Composition

ZYKADIA capsules are available in one dosage strength, 150 mg, containing 150 mg of ceritinib.

Packaging

ZYKADIA is supplied in blister packaging: 150 capsules (3 packs of 50 capsules).

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

ALK Testing

In order to receive ZYKADIA, patients must have a documented ALK-positive status for locally advanced or metastatic NSCLC based on a validated ALK assay. In Study X2101, 99% of patients were demonstrated to have documented ALK positive status by retrospective collection of ALK test pathological reports (See 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 14 CLINICAL TRIALS sections). In Study A2303, 99.1% of patients were demonstrated to have documented ALK positive status at time of study enrollment. In Study A2301, all randomized patients had centrally confirmed ALK-positive status using the VENTANA ALK (D5F3) CDx Assay (Ventana immunohistochemistry [IHC] test). The clinical benefit of ZYKADIA in patients with ALK-negative NSCLC has not been established; therefore, ZYKADIA is not recommended for these patients.

Drug Interactions

Ceritinib is a substrate of CYP3A. Concurrent use of strong CYP3A inhibitors, such as ketoconazole, may increase ceritinib plasma concentration and should be avoided. The concurrent use of strong CYP3A

inducers, such as rifampin, may decrease ceritinib plasma concentration and should be avoided. Ceritinib may inhibit CYP3A and CYP2C9 at clinical concentrations. The concurrent use of CYP3A and CYP2C9 substrates with narrow therapeutic indices or substrates primarily metabolized by CYP3A and CYP2C9 should be avoided (see 6 DOSAGE FORMS, STRENGTHS, and COMPOSITION AND PACKAGING).

Carcinogenesis and Mutagenesis

Carcinogenicity studies have not been performed with ceritinib. Ceritinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay. Ceritinib was not clastogenic in the in vivo rat micronucleus assay. However, ceritinib induced numerical aberrations (aneugenic) in the in vitro cytogenetic assay using human lymphocytes, and micronuclei in the in vitro micronucleus test using TK6 cells. (See 16 NON-CLINICAL TOXICOLOGY).

Cardiovascular

Bradycardia

Bradycardia adverse events (including bradycardia and sinus bradycardia), all Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2, were reported in 2.3% of patients in the pooled analysis comprised of 925 patients with ALK+ advanced NSCLC treated with ZYKADIA at a fasted dose of 750 mg daily across seven clinical studies. Based on ECG data, there were 4.4% of patients in the ceritinib arm having a decrease in heart rate (HR) more than 25% and less than 50 beats per minute compared to baseline. Bradycardia led to dose adjustments or interruptions in 0.2% of patients (see 8 ADVERSE REACTIONS, 9 DRUG INTERACTIONS, 4 DOSAGE AND ADMINISTRATION, 10 CLINICAL PHARMACOLOGY).

Caution should be exercised in patients with a low heart rate at baseline (<60 beats per minute), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular block, ischemic heart disease, or congestive heart failure. Avoid use of ZYKADIA in combination with other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible (see 8 ADVERSE REACTIONS, 9 DRUG INTERACTIONS, 4 DOSAGE AND ADMINISTRATION, 10 CLINICAL PHARMACOLOGY). 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 reduce the dose of ZYKADIA if necessary. Permanently discontinue ZYKADIA for life-threatening bradycardia if no contributing concomitant medication is identified; however, if associated with concomitant medication known to cause bradycardia or hypotension, withhold ZYKADIA until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, and if concomitant medication can be adjusted or discontinued, reinitiate ZYKADIA by reducing dose by 150 mg upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring (see 4 DOSAGE AND ADMINISTRATION and 8 ADVERSE REACTIONS).

QT Interval Prolongation

QTc prolongation occurs in patients treated with ZYKADIA (see 8 ADVERSE REACTIONS, 9 DRUG INTERACTIONS, 4 DOSAGE AND ADMINISTRATION, 10 CLINICAL PHARMACOLOGY).

In a pooled analysis of seven clinical studies comprised of 925 patients with ALK+ advanced NSCLC treated with ZYKADIA at a fasted dose of 750 mg daily, a categorical outlier analysis of ECG data in 919 patients with available data demonstrated new QTc >500 msec in 12 patients (1.3%) among which six had elevated QTc>450 msec at baseline. There were 58 patients (6.3%) with a QTc increase from baseline >60 msec.

A pharmacokinetic/pharmacodynamic analysis suggested that ceritinib causes concentration-dependent increases in QTc (see 10 CLINICAL PHARMACOLOGY).

QTc prolongation may lead to an increased risk of ventricular arrhythmias including torsade de pointes. Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death. Treatment with ZYKADIA is not recommended in patients with congenital long QT syndrome, or who are taking medicinal products known to prolong the QTc interval (see 9 DRUG INTERACTIONS). Hypokalemia, hypomagnesemia, and hypocalcemia must be corrected prior to ZYKADIA administration.

Particular care should be exercised when administering ZYKADIA to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug.

Risk factors for torsade de pointes in the general population include, but are not limited to, the following: female gender; age ≥ 65 years; baseline prolongation of the QT/QTc interval; presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at <50 years of age; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, cardiomyopathy, conduction system disease); history of arrhythmias; electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) or conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders); bradycardia; acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma); diabetes mellitus; and autonomic neuropathy.

Monitor electrocardiogram and electrolytes regularly. Permanently discontinue ZYKADIA in patients who develop torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. Withhold ZYKADIA in patients who develop QTc greater than 500 msec on at least 2 separate ECGs until recovery to baseline or a QTc less than 481 msec, then reinitiate ZYKADIA by reducing dose by 150 mg (see 8 ADVERSE REACTIONS and 10 CLINICAL PHARMACOLOGY).

When drugs that prolong the QTc interval are prescribed, health professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug. Patients should be advised to contact their health professional immediately to report any new chest pain or discomfort, changes in heartbeat, palpitations, dizziness, light headedness, fainting, or changes in or new use of other medications.

Endocrine and Metabolism

Hyperglycemia

In a pooled analysis of seven clinical studies comprised of 925 patients with ALK+ advanced NSCLC, hyperglycemia (all grades) has been reported in 9.4% of patients treated with ZYKADIA at a fasted dose of 750 mg daily; 5.4% of patients reported a Grade 3/4 event.

The risk of hyperglycemia was higher in patients with diabetes mellitus and/or concurrent steroid use.

Monitor fasting serum glucose prior to the start of ZYKADIA treatment and periodically thereafter as clinically indicated. Initiate or optimize anti-hyperglycemic medications as indicated. Based on the severity of hyperglycemia, interruption of ZYKADIA treatment and/or dose reduction may be required. Permanently discontinue ZYKADIA if adequate glycemic control cannot be achieved with optimal

medical management (See 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, 8 ADVERSE REACTIONS and 4 DOSAGE AND ADMINISTRATION).

Gastrointestinal

In a pooled analysis of seven clinical studies comprised of 925 patients with ALK+ advanced NSCLC, gastrointestinal toxicity (nausea, vomiting and diarrhea all grades) occurred in 94.8% of patients treated with ZYKADIA at a fasted dose of 750 mg. Diarrhea, nausea and vomiting occurred in 82.1%, 74.7% and 63.2% of patients, respectively. Persistent Grade 1/2 nausea, vomiting and diarrhea requiring dose reduction have been observed. Grade 3/4 (severe) diarrhea, nausea and vomiting occurred in 5.2%, 5.3% and 5.6% of patients, respectively. Nausea led to dose discontinuation in 0.5%, vomiting in 0.4%, and diarrhea in 0.1% of patients. Diarrhea, nausea and vomiting led to dose adjustments or interruptions in 15.0%, 16.8% and 19.2% of patients, respectively.

Diarrhea, nausea, or vomiting occurred in 76.9% of 108 patients treated with ZYKADIA at the recommended dose of 450 mg taken with food in a dose optimization study A2112 (ASCEND-8) and were mainly grade 1 events (52.8%) and grade 2 (22.2%) events. Two patients (1.9%) experienced one grade 3 event each (diarrhea and vomiting). Nine patients (8.3%) required study drug interruption due to diarrhea or nausea or vomiting. One patient (0.9) required dose adjustment due to vomiting. No patients required dose reduction or discontinuation of ZYKADIA due to diarrhea, nausea, or vomiting (see 8 ADVERSE REACTIONS).

Monitor and manage patients using standards of care, including anti-diarrheals, anti-emetics, or fluid replacement, as indicated. Dose interruption and/or reduction may be employed (see 4 DOSAGE AND ADMINISTRATION and 8 ADVERSE REACTIONS). If vomiting occurs during the course of treatment, the patient should not take an additional dose, but should continue with the next scheduled dose.

The pivotal Studies X2101, A2301 and A2303 excluded patients if they had unresolved nausea, vomiting or diarrhea > CTCAE Grade 1.

Hepatic/Biliary/Pancreatic

Hepatotoxicity

In the pooled analysis of seven clinical studies comprised of 925 patients with ALK+ advanced NSCLC treated with ZYKADIA at a fasted dose of 750 mg daily, hepatotoxicity grouped AEs were reported in 60.5%, and the most frequently reported AEs (in ≥ 5% of patients) were: alanine aminotransferase (ALT) increased (51.0%), aspartate aminotransferase (AST) increased (43.4%), and gamma-glutamyl transferase (GGT) increased (20.8%).

Grade 3/4 hepatotoxicity grouped AEs were reported in 37.8% of patients. The most frequently reported (>10%) Grade 3/4 hepatotoxicity grouped AEs were elevations in liver function tests - ALT increased (25.0%), GGT increased (15.2%), and AST increased (12.6%).

The hepatotoxicity grouped AEs were managed by dose interruptions or adjustments of ceritinib treatment in 40.6% and led to discontinuation of ceritinib treatment in 1.0% of patients. The events were serious in 2.5%, and the most frequently reported (>0.5%) were ALT increased (1.1%) and AST increased (0.9%). There were no deaths due to a hepatotoxicity grouped AE.

Concurrent elevations in ALT or AST greater than three times the upper limit of normal (ULN) and total bilirubin greater than two times the ULN, with normal alkaline phosphatase, occurred in less than 1% of patients in clinical studies.

Monitor liver laboratory tests (including ALT, AST, and total bilirubin) prior to the start of treatment and

monthly thereafter. In patients who develop transaminase elevations, more frequent monitoring of liver transaminases and total bilirubin should be done as clinically indicated. Based on the severity of the adverse drug reactions, dose interruption and reduction or discontinuation of ZYKADIA may be required (see 4 DOSAGE AND ADMINISTRATION, 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 8 ADVERSE REACTIONS).

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 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY). No dose adjustment is recommended in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

Pancreatic Toxicity

ZYKADIA has demonstrated pancreatic toxicity in non-clinical studies (see 16 NON-CLINICAL TOXICOLOGY).

In a pooled analysis of seven clinical studies comprised of 925 patients with ALK+ advanced NSCLC treated with ZYKADIA at a fasted dose of 750 mg daily, the event of pancreatitis was reported in 0.5% of patients, all serious with one fatality. Pancreatitis related events (such as events of pancreatitis, lipase and amylase increased) were reported in 9.6% of patients, 5.8% of which were Grade 3/4, and 0.6% were serious.

Lipase and amylase should be monitored prior to the start of ZYKADIA treatment and periodically thereafter as clinically indicated. Patients should be observed carefully for signs and symptoms of pancreatitis. If pancreatitis is suspected, ZYKADIA should be interrupted or discontinued and appropriate management should be initiated (see 4 DOSAGE AND ADMINISTRATION, 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 8 ADVERSE REACTIONS).

Monitoring and Laboratory Tests

ALK Testing

In order to receive ZYKADIA, patients must have a documented ALK-positive status for locally advanced or metastatic NSCLC based on a validated ALK assay. Assessment for ALK positive locally advanced or metastatic NSCLC should have been performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance can lead to unreliable test results. In Study X2101 and Study A2303, 99% and 99.1% of patients were demonstrated to have documented ALK positive status by retrospective collection of ALK test pathological reports (See 14 CLINICAL TRIALS). In Study A2301, all randomized patients had centrally confirmed ALK-positive status using the VENTANA ALK (D5F3) CDx Assay (Ventana immunohistochemistry [IHC] test). The clinical benefit of ZYKADIA in patients with ALK-negative NSCLC has not been established; therefore, ZYKADIA is not recommended for these patients.

Cardiac Safety Monitoring

Monitor heart rate and blood pressure regularly. Patients receiving ZYKADIA should be monitored for heart rate and blood pressure. ECG evaluations should be performed at baseline prior to initiating therapy with ZYKADIA and should be repeated periodically during treatment with ZYKADIA, to monitor for decreased heart rate and QTc prolongation (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 10 CLINICAL PHARMACOLOGY, 10.2 Pharmacodynamics, Cardiac Electrophysiology). Consultation with a cardiologist should be considered when assessing the QT interval to ensure appropriate treatment decisions.

Electrolyte levels (potassium, calcium, and magnesium) should be assessed at baseline and monitored periodically during treatment with ZYKADIA, particularly in patients at risk for these electrolyte abnormalities (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 9 DRUG INTERACTIONS). Hypokalemia, hypocalcemia, and hypomagnesia should be corrected prior to ZYKADIA administration.

Glucose Monitoring

Monitor fasting serum glucose prior to the start of ZYKADIA treatment and periodically thereafter as clinically indicated. Initiate or optimize anti-hyperglycemic medications as indicated (see 7 WARNINGS AND PRECAUTIONS, 4 DOSAGE AND ADMINISTRATION and 8 ADVERSE REACTIONS).

Lipase and Amylase Monitoring

Monitor lipase and amylase prior to the start of ZYKADIA treatment and periodically thereafter as clinically indicated (See 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; 4 DOSAGE AND ADMINISTRATION and 8 ADVERSE REACTIONS).

Liver Function Test Monitoring

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

Renal Monitoring

Monitor creatinine prior to the start of ZYKADIA treatment and periodically thereafter as clinically indicated (See 8 ADVERSE REACTIONS).

Renal

Renal impairment: ZYKADIA has not been evaluated in patients with renal impairment in a dedicated study. However, based upon available data, ceritinib elimination via the kidney is negligible. Dose adjustment is not required for patients with mild and moderate renal impairment based upon the results of the population pharmacokinetic analyses. Caution should be used in patients with severe renal impairment as there is no experience with ZYKADIA in this population (see 10 CLINICAL PHARMACOLOGY).

Reproductive Health: Female and Male Potential

- **Fertility**

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

- **Teratogenic Risk**

  Based on its mechanism of action, ZYKADIA may cause fetal harm when administered to a pregnant woman (see 7.1 Special Populations and 16 NON-CLINICAL TOXICOLOGY). Advise females of reproductive potential to use highly effective contraception during treatment with ZYKADIA and for up to 3 months following completion of therapy.

Respiratory

Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis have been observed in patients treated with ZYKADIA. In a pooled analysis of seven clinical studies comprised of 925 patients with ALK+ advanced NSCLC treated with ZYKADIA at a fasted dose of 750 mg daily, ILD/pneumonitis AEs were reported in 2.4% of patients – pneumonitis in 1.6%, ILD in 0.4% and lung infiltration in 0.3%.

Grade 3/4 AEs were reported in 1.3% of patients – pneumonitis in 1.0%, ILD in 0.2% and lung infiltration in 0.1%.

The events required dose adjustment or interruption in 1.2% and led to discontinuation of ceritinib treatment in 1.1% of patients. The events were serious in 1.7% of patients. Two deaths due to pneumonitis were reported.

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 4 DOSAGE AND ADMINISTRATION and 8 ADVERSE REACTIONS).

7.1 Special Populations

7.1.1 Pregnant Women

There are no data regarding the use of ZYKADIA in pregnant women. ZYKADIA may cause fetal harm when administered to a pregnant woman. 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 (approximately 0.72-fold the human exposure by AUC at the recommended dose). In addition, embryolethality was observed in rabbits at a dose of 50 mg/kg (approximately equivalent to human exposure by AUC at the recommended dose). The potential risk in humans is unknown. ZYKADIA should not be given to pregnant women unless the potential benefit outweighs the potential risk to the fetus.

Women of childbearing potential

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

If ZYKADIA is used during pregnancy, or if the patient or their partner becomes pregnant while receiving ZYKADIA, then the patient or their partner should be appraised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

Males

Adequate contraceptive methods should be used by men during therapy, and for at least 3 months after completing therapy. If the patient's partner becomes pregnant while receiving ZYKADIA, then the patient and his partner should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy.

7.1.2 Breast-feeding

It is unknown whether ceritinib is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse drug reactions in breastfed newborns/infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of ZYKADIA have not been established in pediatric patients.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): Across seven clinical studies in patients with ALK+ advanced NSCLC receiving a fasted dose of 750 mg daily, 168 of 925 patients (18.2%) treated with ZYKADIA were aged 65 years and older. No overall differences in safety or efficacy were observed between younger (<65 years) and older patients (≥ 65 years).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse events (AEs) regardless of study drug relationship described below reflect exposure to ZYKADIA in 925 patients with ALK-positive advanced NSCLC treated at a fasted dose of 750 mg taken orally once daily in seven clinical studies including studies A2301, X2101 and A2303 described below.

The median duration of exposure to ZYKADIA 750 mg fasted was 44.9 weeks (range 0.1 to 200.1 weeks).

Adverse events with an incidence of ≥20% of 925 pooled patients treated with ZYKADIA 750 mg fasted were diarrhea (82.1%), nausea (74.7%), vomiting (63.2%), alanine aminotransferase increased (51.0%), aspartate aminotransferase increased (43.4%), decreased appetite (39.5%), fatigue (33.9%), abdominal pain (31.0%), weight decreased (27.6%), constipation (24.0%), cough (23.4%), blood creatinine increased (22.1%), blood alkaline phosphatase (21.6%), gamma-glutamyl transferase increased (20.8%), headache (20.6%) and dyspnea (20.2%).

In the pooled analysis of 925 patients treated with ZYKADIA 750 mg fasted, serious adverse events (SAEs) regardless of study drug relationship were reported in 409 patients (44.2%). The most frequently reported SAEs in ≥ 1% of the patients were: pneumonia, dyspnea, nausea, vomiting, pleural effusion, seizure, pericardial effusion, pyrexia, hyperglycemia, respiratory failure, general physical health deterioration, dehydration, lung infection, pneumonitis, pulmonary embolism, pericarditis, ALT increased, asthenia, non-cardiac chest pain and diarrhea.

Adverse events requiring dose adjustment or interruption were reported in 715 patients (77.3%), among whom 498 patients (53.8%) had a grade 3/4 AE. The most frequently occurring (any grade, in ≥ 5% of the patients) AEs requiring dose adjustment or interruption were ALT increased (34.8%), AST increased (22.8%), vomiting (19.2%), nausea (16.8%), diarrhea (15.0%), blood creatinine increased (6.9%), fatigue (6.4%), decreased appetite and GGT increased (each 5.6%).

Among the 925 patients in the pooled analysis, the proportion of patients with AEs leading to permanent discontinuation of ceritinib treatment was 12.1%.The most frequent AEs (>0.5%) leading to

discontinuation of ZYKADIA 750 mg fasted were pneumonia (0.6%) and respiratory failure (0.6%).

In the dose optimization study A2112 (ASCEND-8) in both previously treated and untreated patients with ALK-positive advanced NSCLC, the overall safety profile of ZYKADIA at the recommended dose of 450 mg with food (N=108) was consistent with ZYKADIA 750 mg fasted (N=110), except for a reduction in gastrointestinal adverse drug reactions, while achieving comparable steady-state exposure (see 10 CLINICAL PHARMACOLOGY).

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Previously Untreated ALK-positive Locally Advanced or Metastatic NSCLC

Phase III study A2301

Study A2301 was an open-label, randomized, active-controlled, global, Phase III study of ceritinib (750 mg daily under fasted conditions) versus standard first-line chemotherapy (cisplatin or carboplatin with pemetrexed administered every 21 days for 4 cycles followed by pemetrexed maintenance in patients without progressive disease) in adult patients with ALK+ advanced NSCLC. Patients in the chemotherapy arm were allowed to receive ZYKADIA after BIRC-confirmed disease progression (see 14 CLINICAL TRIALS).

Overall, the majority of the patients were Caucasian (53.7%) or Asian (42.0%). The median age was 54.0 years (range: 22 to 81 years); 78.5% of patients were younger than 65 years. The majority of patients had adenocarcinoma (96.5%) and had never smoked (61.2%). The (Eastern Cooperative Oncology Group) ECOG performance status was 0/1/2 in 37.0%/56.4%/6.4% of patients respectively, and 32.2% had stable brain metastasis at baseline (see 14 CLINICAL TRIALS).

Ten patients (5.3%) in the ceritinib arm and nine patients (4.8%) in the chemotherapy arm received prior chemotherapy in the neo-adjuvant/adjuvant setting.

The median duration of exposure to the study drug was higher in the ZYKADIA arm (66.4 weeks, range: 1.0 to 144.4) compared to chemotherapy arm including pemetrexed (26.9 weeks, range: 0.7 to 126.7).

The safety population comprised patients who received at least one dose of study drug (189 in the ceritinib arm and 175 in the chemotherapy arm). All patients (100%) in the ceritinib arm and 170 patients (97.1%) in the chemotherapy arm experienced at least one AE during the treatment phase.

The most frequently reported adverse events regardless of study drug relationship in the ZYKADIA arm (in ≥ 10% of patients) included: diarrhea, nausea, vomiting, ALT increased, AST increased, GGT increased, blood ALP increased, decreased appetite, fatigue, abdominal pain, cough, weight decreased, blood creatinine increased, abdominal pain upper, non-cardiac chest pain, constipation, back pain, pyrexia, asthenia, headache, dyspnea, anemia, rash, dizziness, musculoskeletal pain, electrocardiogram QT prolonged, hyperglycemia, pain in extremity, pruritus and amylase increased.

Serious adverse events (SAE) regardless of study drug relationship were reported in 37.0% of patients in the ZYKADIA arm and 35.4% of patients in the chemotherapy arm, majority of whom were noted with grade 3/4 AEs (31.2% in ZYKADIA arm vs. 30.3% in chemotherapy arm). The most frequently reported SAEs in the ZYKADIA arm (>1%) were pneumonia, pleural effusion, vomiting, nausea, dyspnea, hyperglycemia, AST increased, pericardial effusion, ALT increased, diarrhea, back pain, lung infection,

pulmonary embolism, blood creatinine increased, metastases to central nervous system, pyrexia, general physical health deterioration, fatigue, non-cardiac chest pain, atrial fibrillation, dizziness, malaise, paresthesia and hepatic function abnormal.

Adverse events that required dose adjustment or interruption were 80.4% and 44.6% in the ZYKADIA arm and chemotherapy arm, respectively. The most frequent adverse events regardless of study drug relationship reported in at least 10% of patients that led to dose adjustment or interruption were ALT increased (47.6%), AST increased (33.9%), vomiting (15.3%), blood creatinine increased (13.8%), GGT increased (13.2%), diarrhea (12.7%) and nausea (11.6%) in the ZYKADIA arm and neutropenia (10.3%) in the chemotherapy arm.

Adverse events regardless of study drug relationship that led to treatment discontinuation were reported in 21 patients (11.1%) in the ZYKADIA arm and 29 patients (16.6%) in the chemotherapy arm. The adverse events reported (in ≥ 1% of the patients) leading to discontinuation of study treatment regardless of study drug relationship were blood creatinine increased (2.1%), lipase increased (1.1%) and amylase increased (1.1%) in the ZYKADIA arm and blood creatinine increased (3.4%), creatinine renal clearance decreased (1.7%), dyspnea (1.1%) and tinnitus (1.1%) in the chemotherapy arm.

On-treatment deaths were reported in 11 patients (5.8%) in the ZYKADIA arm, 7 due to disease progression and 4 patients due to AEs (one each for myocardial infarction, respiratory tract infection, pneumonitis, and unknown cause).

Table 3 lists the incidences of very common and common adverse reactions in patients receiving ZYKADIA 750 mg fasted in Study A2301.

Table 3 Adverse drug reactions ≥ 1% in patients treated with ZYKADIA at a dose of 750 mg fasted in Study A2301

Primary System Organ Class Preferred Term	**ZYKADIA N=189 n (%)**		**Chemotherapy N=175 n (%)**	
	All Grades n (%)	**Grades 3/4 n (%)**	**All Grades n (%)**	**Grades 3/4 n (%)**
Blood And Lymphatic System Disorders				
Anemia	28 (14.8)	4 (2.1)	62 (35.4)	13 (7.4)
Cardiac Disorders				
Bradycardia[e]	6 (3.2)	0	1 (0.6)	0
Pericarditis[h]	8 (4.2)	3 (1.6)	3 (1.7)	2 (1.1)
Eye Disorders				
Vision disorder[l]	7 (3.7)	0	7 (4.0)	0
Gastrointestinal Disorders				
Abdominal Pain[a]	75 (39.7)	7 (3.7)	20 (11.4)	0
Constipation	36 (19.0)	0	38 (21.7)	0
Diarrhea	160 (84.7)	10 (5.3)	19 (10.9)	2 (1.1)

Primary System Organ Class Preferred Term	ZYKADIA N=189 n (%)		Chemotherapy N=175 n (%)	
	All Grades n (%)	Grades 3/4 n (%)	All Grades n (%)	Grades 3/4 n (%)
Nausea	130 (68.8)	5 (2.6)	97 (55.4)	9 (5.1)
Esophageal disorder[f]	28 (14.8)	1 (0.5)	13 (7.4)	1 (0.6)
Vomiting	125 (66.1)	10 (5.3)	63 (36.0)	10 (5.7)
General Disorders And Administration Site Conditions				
Fatigue[g]	83 (43.9)	13 (6.9)	85 (48.6)	11 (6.3)
Back pain	36 (19.0)	3 (1.6)	32 (18.3)	4 (2.3)
Pain in extremity	21 (11.1)	0	13 (7.4)	0
Hepatobiliary Disorders				
Abnormal liver function tests[c]	3 (1.6)	2 (1.1)	2 (1.1)	1 (0.6)
Hepatotoxicity[d]	4 (2.1)	1 (0.5)	1 (0.6)	0
Investigations				
Amylase Increased	19 (10.1)	9 (4.8)	9 (5.1)	3 (1.7)
Blood Creatinine Increased	42 (22.2)	4 (2.1)	17 (9.7)	0
Electrocardiogram QT Prolonged	21(11.1)	4 (2.1)	2 (1.1)	1 (0.6)
Lipase Increased	7 (3.7)	7 (3.7)	0	0
Liver laboratory test abnormalities[b]	130 (68.8)	94 (49.7)	50 (28.6)	10 (5.7)
Weight Decreased	45 (23.8)	7 (3.7)	26 (14.9)	1 (0.6)
Metabolism And Nutrition Disorders				
Decreased Appetite	64 (33.9)	2 (1.1)	55 (31.4)	2 (1.1)
Hyperglycemia	21 (11.1)	12 (6.3)	13 (7.4)	5 (2.9)
Hypophosphatemia	8 (4.2)	3 (1.6)	0	0
Renal And Urinary Disorders				
Renal Failure[k]	4 (2.1)	0	3 (1.7)	1 (0.6)
Respiratory, Thoracic And Mediastinal Disorders				
Pneumonitis[i]	3 (1.6)	1 (0.5)	0	0
Skin And Subcutaneous Tissue Disorders				

Primary System Organ Class Preferred Term	ZYKADIA N=189 n (%)		Chemotherapy N=175 n (%)	
	All Grades n (%)	Grades 3/4 n (%)	All Grades n (%)	Grades 3/4 n (%)
Rash[j]	38 (20.1)	2 (1.1)	14 (8.0)	1 (0.6)

Includes cases reported within the clustered terms:

[a] Abdominal pain includes PTs of Abdominal Pain, Abdominal Pain Upper, Abdominal Discomfort, Epigastric Discomfort

[b] Liver laboratory test abnormalities includes PTs of Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Gamma-Glutamyltransferase Increased, Blood Bilirubin Increased, Transaminases Increased, Hepatic Enzyme Increased, Liver Function Test Abnormal, Liver Function Test Increased, Blood Alkaline Phosphatase Increased

[c] Abnormal liver function tests includes PTs of Hepatic Function Abnormal, Hyperbilirubinemia

[d] Hepatotoxicity includes PTs of Drug-Induced Liver Injury, Hepatitis Cholestatic, Hepatocellular Injury, Hepatotoxicity

[e] Bradycardia includes PTs of Bradycardia and Sinus Bradycardia

[f] Esophageal Disorder includes PTs of Dyspepsia, Gastroesophageal Reflux Disease, Dysphagia

[g] Fatigue includes PTs of Fatigue and Asthenia

[h] Pericarditis includes PTs of Pericardial Effusion and Pericarditis

[i] Pneumonitis includes PTs of Interstitial Lung Disease (ILD) and Pneumonitis

[j] Rash includes PTs of Rash, Dermatitis Acneiform, Rash Maculo-Papular

[k] Renal Failure includes PTs of Acute Renal Injury and Renal Failure

[l] Vision disorder includes PTs of Visual Impairment, Vision Blurred, Photopsia, Vitreous Floaters, Visual Acuity Reduced, Accommodation Disorder, Presbyopia

Previously Treated ALK-positive Locally Advanced or Metastatic NSCLC

Phase I Study X2101

Study X2101 was a single arm, phase I, open-label, dose-escalation and expansion study investigating the safety, pharmacokinetics, and anti-tumor activity of ZYKADIA in patients with tumors confirmed to have genetic abnormalities in ALK. Adverse drug reaction (ADR) information is based on safety data from this registration study in 255 patients (246 ALK-positive NSCLC patients and 9 non-NSCLC patients) treated at a dose of 750 mg of ZYKADIA under fasted conditions.

The Study X2101 population characteristics were: median age 53 years, age less than 65 (84.3%), female (53.3%), Caucasian (62.7%), Asian (34.1%), Others (3.1%), NSCLC adenocarcinoma histology (89.8%), never or former smoker (96.9%), ECOG PS 0 or 1 (88.6%), brain metastasis (48.6%), and number of prior therapies 2 or more (66.7%).

The median exposure to ZYKADIA was 43.0 weeks (range: 0.4 to 200.1 weeks). The median dose intensity was 610.3 mg/day (range: 226.5 mg/day to 750 mg once daily fasted). Dosing interruptions due to adverse events occurred in 88.9% of patients. Dose reductions due to adverse events occurred in 97.5% of patients. The most frequent adverse events reported in at least 10% of patients that led to dose reduction or interruption were ALT increased (32.5%), nausea (20.8%), diarrhea (19.2%), AST increased (18.8%), and vomiting (18.0%).

In Study X2101, 54.5% of patients permanently discontinued the treatment due to disease progression and 11.0% due to an AE as primary reason for discontinuation. The most frequent AEs that led to discontinuation in more than 1 patient were pneumonia (1.6%), respiratory failure (1.2%), pneumonitis (0.8%), decreased appetite (0.8%), general physical health deterioration (0.8%), and nausea (0.8%).

In Study X2101, 56.9% of patients reported a SAE. SAEs with an incidence of ≥1% were: pneumonia (7.5%), seizure (6.3%), dyspnea (5.9%), pneumonitis (3.5%), respiratory failure (2.4%), pericardial effusion (2.4%), general physical health deterioration (2.4%), hyperglycemia (2.4%), nausea (2.4%), ALT increased (2.0%), headache (2.0%), pericarditis (2.0%), dehydration (1.6%), pneumothorax (1.6%), non-cardiac chest pain (1.6%), pyrexia (1.6%), vomiting (1.2%), AST increased (1.2%), pulmonary embolism (1.2%), ataxia (1.2%), diarrhea (1.2%), pleural effusion (1.2%), and sepsis (1.2%).

Deaths in patients during treatment or within 28 days of last dose with ZYKADIA occurred in 17.3% including 11.8% of deaths due to study indication and 5.5% of patients, consisting of: pneumonia (3 patients), respiratory failure (3 patients), ILD/pneumonitis, pneumothorax, gastric hemorrhage, pulmonary tuberculosis, cardiac tamponade, multi-organ failure, euthanasia and sepsis (1 patient each).

Table 4 lists the incidences of very common and common adverse reactions in patients receiving ZYKADIA 750 mg fasted in Study X2101.

Table 4 Adverse drug reactions ≥1% in patients treated at a dose of 750 mg fasted in Study X2101

Primary System Organ Class Preferred Term	**ZYKADIA N=255 n (%)**	
	All Grades	**Grade 3/4**
Blood and lymphatic system disorders		
Anemia	34 (13.3)	13 (5.1)
Cardiac disorders		
Bradycardia[a]	9 (3.5)	0
Eye disorders		
Vision disorder[b]	34 (13.3)	0
Gastrointestinal disorders		
Diarrhea	221 (86.7)	16 (6.3)
Nausea	216 (84.7)	17 (6.7)
Vomiting	160 (62.7)	15 (5.9)
Abdominal pain[c]	145 (56.9)	6 (2.4)
Constipation	91 (35.7)	0
Esophageal disorder[d]	55 (21.6)	2 (0.8)
General disorders and administration site conditions		
Fatigue[e]	148 (58)	17 (6.7)
Investigations		
Alanine aminotransferase increased	122 (47.8)	81 (31.8)

Primary System Organ Class Preferred Term	ZYKADIA N=255 n (%)	
	All Grades	**Grade 3/4**
Aspartate aminotransferase increased	91 (35.7)	36 (14.1)
Blood creatinine increased	48 (18.8)	0
Lipase increased	35 (13.7)	23 (9.0)
Electrocardiogram QT prolonged	12 (4.7)	3 (1.2)
Blood bilirubin increased	10 (3.9)	1 (0.4)
Metabolism and nutrition disorders		
Decreased appetite	99 (38.8)	5 (2.0)
Hyperglycemia	26 (10.2)	17 (6.7)
Hypophosphatemia	19 (7.5)	10 (3.9)
Nervous system disorders		
Neuropathy[f]	44 (17.3)	0
Renal and urinary disorders		
Renal failure[g]	6 (2.4)	1 (0.4)
Renal impairment[h]	5 (2.0)	1 (0.4)
Respiratory, thoracic and mediastinal disorders		
Pneumonitis[i]	12 (4.7)	9 (3.5)
Skin and subcutaneous tissue disorders		
Rash[j]	50 (19.6)	0

Includes cases reported within the clustered terms:
[a] Bradycardia (bradycardia, sinus bradycardia)
[b] Vision disorder (vision impairment, vision blurred, photopsia, vitreous floaters, accommodation disorder, presbyopia, visual acuity reduced)
[c] Abdominal pain (abdominal pain, abdominal pain upper, abdominal discomfort, epigastric discomfort)
[d] Esophageal disorder (dyspepsia, gastroesophageal reflux disease, dysphagia)
[e] Fatigue (fatigue, asthenia)
[f] Neuropathy (paraesthesia, muscular weakness, gait disturbance, neuropathy peripheral, hypoaesthesia, peripheral sensory neuropathy, dysaesthesia, neuralgia, peripheral motor neuropathy, hypotonia, polyneuropathy)
[g] Renal failure (acute kidney injury, renal failure)
[h] Renal impairment (azotemia, renal impairment)
[i] Pneumonitis (interstitial lung disease, pneumonitis)
[j] Rash (rash, rash maculo-papular, dermatitis acneiform)

Phase III Study A2303

Study A2303 was a Phase III, randomized, open-label study of ZYKADIA versus standard chemotherapy (pemetrexed/docetaxel) in adult patients. Patients in the chemotherapy arm were allowed to cross-over to the ZYKADIA 750 mg fasted arm after BIRC-confirmed PD. Adverse drug reaction (ADR) information is based on safety data from this registration study in 115 patients.

In Study A2303, population characteristics were: median age 54.0 years (range: 28 to 84 years), age less than 65 (77.1%), female (55.8%), Caucasians (64.5%), Asians (29.4%), Blacks (0.4%) and other races (2.6%). The majority of patients had adenocarcinoma (97.0%) and had either never smoked or were former smokers (96.1%). The ECOG performance status was 0/1/2 in 46.3%/47.6%/6.1% of patients respectively, and 58.0% had brain metastasis at baseline. All patients were treated with prior crizotinib. All except one patient received prior chemotherapy (including a platinum doublet) for advanced disease; 11.3% of the patients in the ZYKADIA arm and 12.1% of the patients in the chemotherapy arm were treated with two prior chemotherapy regimens for advanced disease.

The median duration of exposure to the study drug was higher in the ZYKADIA arm (30.3 weeks, range: 0.3 to 122.9) compared to chemotherapy arm (6.3 weeks, range: 3.0 to 69.1; pemetrexed: 14.1 weeks, range: 3.0 to 69.1; docetaxel: 6.1 weeks, range: 3.0 to 36.0).

The safety population comprised patients who received at least one dose of study drug (115 in the ceritinib arm and 113 in the chemotherapy arm). All patients (100%) in the ceritinib arm and all but one (99%) patient in the chemotherapy arm experienced at least one AE during the treatment phase. The overall incidence of severe (Grade 3/4) adverse events was higher in the ZYKADIA than in the chemotherapy arm (77% vs 64%) as was the incidence of serious adverse events (43% vs 32%). Adverse events requiring dose modification (reduction, interruption or delay) were reported in 80% of patients in the ZYKADIA arm and 38% of patients in the chemotherapy arm. The most common adverse events requiring dose modifications in the ceritinib arm were hepatotoxicity in 36.5% of patients and GI toxicity in 34.8% of patients.

Table 5 lists the incidences of very common and common adverse reactions in patients receiving ZYKADIA 750 mg fasted in Study A2303.

Table 5 Adverse drug reactions ≥1% in patients treated at a dose of 750 mg fasted in Study A2303

Primary System Organ Class Preferred Term	**ZYKADIA N=115 n (%)**		**Chemotherapy N=113 n (%)**	
	All Grades n (%)	**Grades 3/4 n (%)**	**All Grades n (%)**	**Grades 3/4 n (%)**
Blood And Lymphatic System Disorders				
Anemia	6 (5.2)	0	19 (16.8)	5 (4.4)
Cardiac Disorders				
Pericarditis[g]	8 (7.0)	4 (3.5)	1 (0.9)	1 (0.9)
Bradycardia[d]	3 (2.6)	0	1 (0.9)	0
Eye Disorders				
Vision disorder[l]	4 (3.5)	0	3 (2.7)	1 (0.9)
Gastrointestinal Disorders				
Diarrhea	83 (72.2)	5 (4.3)	20 (17.7)	1 (0.9)
Nausea	76 (66.1)	9 (7.8)	26 (23.0)	2 (1.8)

Primary System Organ Class Preferred Term	ZYKADIA N=115 n (%)		Chemotherapy N=113 n (%)	
	All Grades n (%)	Grades 3/4 n (%)	All Grades n (%)	Grades 3/4 n (%)
Vomiting	60 (52.2)	9 (7.8)	6 (5.3)	1 (0.9)
Abdominal Pain[a]	41 (35.7)	2 (1.7)	17 (15.0)	1 (0.9)
Constipation	22 (19.1)	0	15 (13.3)	0
Esophageal disorder[e]	10 (8.7)	1 (0.9)	4 (3.5)	0
General Disorders And Administration Site Conditions				
Fatigue[f]	54 (47.0)	11 (9.6)	53 (46.9)	12 (10.6)
Back pain	25 (21.7)	1 (0.9)	8 (7.1)	3 (2.7)
Hepatobiliary Disorders				
Abnormal liver function tests[b]	4 (3.5)	0	2 (1.8)	1 (0.9)
Hepatotoxicity[c]	2 (1.7)	0	0	0
Investigations				
Alanine Aminotransferase (ALT) Increased	49 (42.6)	24 (20.9)	10 (8.8)	2 (1.8)
Aspartate Aminotransferase (AST) Increased	42 (36.5)	16 (13.9)	5 (4.4)	1 (0.9)
Weight Decreased	34 (29.6)	3 (2.6)	7 (6.2)	1 (0.9)
Gamma-Glutamyl transferase (GGT) Increased	26 (22.6)	24 (20.9)	2 (1.8)	1 (0.9)
Blood Creatinine Increased	22 (19.1)	0	0	0
Electrocardiogram QT Prolonged	13 (11.3)	1 (0.9)	0	0
Amylase Increased	7 (6.1)	5 (4.3)	3 (2.7)	3 (2.7)
Blood Bilirubin Increased	1 (0.9)	0	1 (0.9)	0
Metabolism And Nutrition Disorders				
Decreased Appetite	48 (41.7)	2 (1.7)	22 (19.5)	3 (2.7)
Hyperglycemia	8 (7.0)	6 (5.2)	3 (2.7)	2 (1.8)
Hypophosphatemia	3 (2.6)	0	4 (3.5)	1 (0.9)
Renal And Urinary Disorders				
Renal Failure[j]	1 (0.9)	0	0	0
Renal Impairment[k]	1 (0.9)	0	0	0

Primary System Organ Class Preferred Term	ZYKADIA N=115 n (%)		Chemotherapy N=113 n (%)	
	All Grades n (%)	Grades 3/4 n (%)	All Grades n (%)	Grades 3/4 n (%)
Respiratory, Thoracic And Mediastinal Disorders				
Pneumonitis[h]	1 (0.9)	1 (0.9)	3 (2.7)	3 (2.7)
Skin And Subcutaneous Tissue Disorders				
Rash[i]	15 (13.0)	0	14 (12.4)	0

Includes cases reported within the clustered terms:

[a]Abdominal Pain, Abdominal Pain Upper, Abdominal Discomfort, Epigastric Discomfort
[b]Hepatic Function Abnormal, Hyperbilirubinaemia
[c]Drug-Induced Liver Injury, Hepatitis Cholestatic, Hepatocellular Injury, Hepatotoxicity
[d]Bradycardia, Sinus Bradycardia
[e]Dyspepsia, Gastrooesophageal Reflux Disease, Dysphagia
[f]Fatigue, Asthenia
[g]Pericardial Effusion Pericarditis
[h]Interstitial Lung Disease, Pneumonitis
[i]Rash, Dermatitis Acneiform, Rash Maculo-Papular
[j]Acute kidney Injury, Renal Failure
[k]Azotaemia, Renal Impairment
[l]Visual Impairment, Vision Blurred, Photopsia, Vitreous Floaters, Visual Acuity Reduced, Accommodation Disorder, Presbyopia

Phase I Study A2112

Study A2112 was a Phase I, randomized, open-label study in which the systemic exposure, efficacy, and safety of ZYKADIA administered once daily at 450 mg or 600 mg with a low-fat meal was assessed versus 750 mg under fasted conditions. Adverse drug reaction (ADR) information is based on safety data from this study in 304 patients.

In Study A2112, population characteristics were: median age 54.0 years (range: 21 to 87 years), age less than 65 (79.7%), female (50.7%), Caucasians (59.8%), Asians (33.3%), Blacks (0.7%) and Other (3.9%). The majority of patients had adenocarcinoma (94.8%) and had either never smoked (59.2%) or were former smokers (34.6%). The WHO performance status was 0/1/2 in 32.7%/58.8%/8.5% of patients respectively, and 35.6% had brain metastasis at baseline.

Overall, 211 patients (69.0%) did not receive any prior regimen of anti-cancer medication (69.4% of patients in the 450 mg fed arm, 64.4% of patients in the 600 mg fed arm and 72.1% of patients in the 750 mg fasted arm). Six (5.6%), five (5.7%), and three patients (2.7%) received at least 3 prior lines of anti-cancer regimens, in the 450 mg fed arm, 600 mg fed arm, and 750 mg fasted arm, respectively. Most frequently used anti-cancer medications (>20.0% of all patients in FAS) were cisplatin (22.5%), crizotinib (21.6%) and pemetrexed (21.2%).

The safety population comprised patients who received at least one dose of study drug (108 in 450 mg fed arm, 86 in 600 mg fed arm and 110 in 750 mg fasted arm.

Overall, the median duration of exposure was 78.21 weeks (range: 0.3 to 228.1) for all treated patients, and was similar across the three treatment arms.

Almost all treated patients (99.0%) reported at least one adverse event; the proportion of patients who experienced one adverse event regardless of study drug relationship was similar across the three treatment arms (100.0% of patients in the 450 mg fed arm, 97.7% in the 600 mg fed arm, and 99.1% in the 750 mg fasted arm).

Overall, 107 (35.2%) patients experienced any grade serious adverse events, regardless of study drug relationship during the on-treatment period with a lower proportion of patients in the 450 mg fed arm (32.4%) and 750 mg fasted arm (30.9%), compared to 600 mg fed arm (44.2%). The proportions of patients with serious adverse events suspected to study drug was low (10.9% patients) specially in the 450 mg fed (7.4%) and the 750 mg fasted (10.9%) treatment arms compared to 15.1% in the 600 mg treatment arm.

The proportion of patients with adverse events that led to study drug discontinuation was similar among treatment arms: 26 (8.6%) patients (nine, seven and ten patients in the 450 mg fed arm, in the 600 mg fed arm and in the 750 mg fasted arm, respectively).

Overall 70.1% of patients were reported with adverse events that required dose adjustment or study drug interruption which was lowest (56.5%) in the 450 mg fed arm compared to 77.9% in the 600 mg fed arm and 77.3% in the 750 mg fasted arm.

The incidence and severity of gastrointestinal adverse drug reactions (diarrhea 59.3%, nausea 42.6%, vomiting 38.0%; 0.9% reported a Grade 3/4 event) were reduced for patients treated with ZYKADIA 450 mg with food compared to 750 mg fasted (diarrhea 80.0%, nausea 60.0%, vomiting 65.5%; 4.5% reported a Grade 3/4 event). In patients treated with ZYKADIA 450 mg with food, 24.1% of patients had at least one adverse event that required dose reduction and 55.6% of patients had at least one adverse event that required study drug interruption.

8.3 Less Common Clinical Trial Adverse Reactions

Less Common Clinical Trial Adverse Drug Reactions (<1%) in study X2101

Gastrointestinal disorders
Uncommon: Pancreatitis

Hepatobiliary disorders
Uncommon: Drug-induced liver injury

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Previously Untreated ALK-positive Locally Advanced or Metastatic NSCLC

Table 6 Key Laboratory Abnormalities Occurring in >10% (All NCI CTCAE Grades) of patients treated with ZYKADIA at a dose of 750 mg fasted in Study A2301

	ZYKADIA N=189		Chemotherapy N=175	
	All Grades	Grade 3/4	All Grades	Grade 3/4
	%	%	%	%
Chemistry				
Alanine transaminase (ALT) increased	92.6	33.9	66.3	3.4
Aspartate transaminase (AST) increased	87.8	20.1	59.4	2.3
Gamma-Glutamyl transferase (GGT) Increased	84.7	48.7	69.1	9.1
Increased alkaline phosphatase	81.5	11.6	46.9	1.7
Creatinine increased	78.8	4.2	37.1	0.6
Glucose increased	51.9	10.1	69.1	10.3
Phosphate decreased	37.6	3.7	27.4	3.4
Amylase increased	37.0	7.4	44.0	4.6
Increased bilirubin (total)	16.4	0.5	6.9	0.6
Hematology				
Hemoglobin decreased	68.8	3.7	85.7	10.9
Neutrophils decreased	28.0	2.1	60.0	19.4
Platelets decreased	17.5	1.0	39.4	5.1

Previously Treated ALK-positive Locally Advanced or Metastatic NSCLC

Table 7 Key Laboratory Abnormalities Occurring in >10% (All NCI CTCAE Grades) of patients treated at a dose of 750 mg fasted in Study X2101

	ZYKADIA N=255	
	All Grades	Grade 3/4
	%	%
Chemistry		
Alanine transaminase (ALT) increased	83.9	32.1
Aspartate transaminase (AST) increased	77.6	18.1
Creatinine increased	51.4	2.4
Glucose increased	58	15.3
Uric acid increased	50.2	9.0
Phosphate decreased	43.9	9.0
Amylase increased	32.9	8.3
Lipase increased	34.1	14.1
Bilirubin (total) increased	20.4	0.8

	ZYKADIA N=255	
	All Grades	Grade 3/4
	%	%
Hematology		
Hemoglobin decreased	85.9	7.1
Lymphocytes decreased	79.2	35.7
Neutrophils decreased	30.6	3.9

Table 8 Key Laboratory Abnormalities Occurring in >10% (All NCI CTCAE Grades) of patients treated at a dose of 750 mg fasted in Study A2303

	ZYKADIA N=115		Chemotherapy N=113	
	All Grades	Grade 3/4	All Grades	Grade 3/4
	%	%	%	%
Chemistry				
Alanine transaminase (ALT) increased	80.9	24.3	45.1	2.7
Creatinine increased	79.1	0	20.3	0
Aspartate transaminase (AST) increased	75.6	14.8	32.7	1.8
Gamma-Glutamyl transferase (GGT) Increased	74.8	40.0	44.2	5.3
Glucose increased	49.6	9.6	46.0	6.2
Phosphate decreased	40.0	5.2	22.1	2.7
Amylase increased	37.4	5.2	26.5	5.3
Hematology				
Lymphocytes decreased	67.0	18.3	60.2	23.9
Hemoglobin decreased	64.3	0.9	50.4	4.4
Neutrophils decreased	20.9	1.7	39.9	26.6

9 DRUG INTERACTIONS

9.1 Drug-Drug Interactions

Drugs That May Increase Ceritinib Plasma Concentrations

CYP3A Inhibitors

Ceritinib is primarily metabolized by CYP3A and is a substrate of CYP3A. Co-administration of a single 450 mg fasted ceritinib dose with ketoconazole (a strong CYP3A/P-gp 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 1.2-fold (1.1, 1.4) in 19 healthy subjects. Avoid concomitant use of strong CYP3A inhibitors, including but not limited to,

ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, and nefazodone. Exercise caution with concomitant use of moderate CYP3A inhibitors and carefully monitor adverse drug reactions.

The steady-state AUC and C_{max} of ceritinib at reduced doses after co-administration with ketoconazole 200 mg twice daily for 14 days was predicted by simulations to be similar to the steady-state AUC and C_{max} of ceritinib alone.

P-gp Inhibitors

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

Drugs That May Decrease Ceritinib Plasma Concentrations

CYP3A and P-gp Inducers

Co-administration of a single 750 mg fasted ceritinib dose with rifampin (a strong CYP3A/P-gp 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. Avoid concomitant use of strong CYP3A inducers, including but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort *(Hypericum perforatum)*. Exercise caution with concomitant use of P-gp inducers.

Drugs Whose Plasma Concentrations May Be Altered by Ceritinib

CYP3A and CYP2C9 Substrates

Based on *in vitro* data, ceritinib competitively inhibits the metabolism of CYP3A and CYP2C9 substrates. Time-dependent inhibition of CYP3A was also observed. Co-administration of a single dose of midazolam (a sensitive CYP3A substrate) following 3 weeks of ZYKADIA dosing in patients (750 mg daily fasted) increased the midazolam AUC_{inf} (90% CI) by 5.4-fold (4.6, 6.3) compared to midazolam alone. Avoid co-administration of ZYKADIA with substrates primarily metabolized by CYP3A or CYP3A substrates known to have narrow therapeutic indices (e.g., cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, tacrolimus, alfentanil, and sirolimus). If unavoidable, consider dose reduction for co-administered medicines that are CYP3A substrates with narrow therapeutic indices.

Co-administration of a single dose of warfarin (a CYP2C9 substrate) following 3 weeks of ZYKADIA dosing in patients (750 mg daily fasted) increased the S-warfarin AUC_{inf} (90% CI) by 54% (36%, 75%) compared to warfarin alone. Avoid co-administration of ZYKADIA with substrates primarily metabolized by CYP2C9 or CYP2C9 substrates known to have narrow therapeutic indices (e.g., phenytoin and warfarin). If unavoidable, consider dose reduction for co-administered medicines that are CYP2C9 substrates with narrow therapeutic indices. Increase the frequency of international normalized ratio (INR) monitoring if co-administration with warfarin is unavoidable as the anti-coagulant effect of warfarin may be enhanced (See Drug Interactions under 16 NON-CLINICAL TOXICOLOGY, DETAILED PHARMACOLOGY).

CYP2A6 and CYP2E1 Substrates

Based on *in vitro* data, ceritinib also inhibits CYP2A6 and CYP2E1 at clinically relevant concentrations. Therefore, ceritinib may have the potential to increase plasma concentrations of co-administered drugs that are predominantly metabolized by these enzymes. Exercise caution with concomitant use of

CYP2A6 and CYP2E1 substrates and carefully monitor adverse drug reactions (See Drug Interactions under 16 NON-CLINICAL TOXICOLOGY, DETAILED PHARMACOLOGY).

Other CYP substrates

In vitro studies indicated that clinical drug-drug interactions are unlikely to occur as a result of ceritinib-mediated inhibition of the metabolism of drugs that are substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C19, and CYP2D6. (See Drug Interactions under 16 NON-CLINICAL TOXICOLOGY, DETAILED PHARMACOLOGY).

Drugs That Are Substrates of Transporters

Based on *in vitro* data, ceritinib does not inhibit apical efflux transporters, BCRP, P-gp or MRP2, hepatic uptake transporters OATP1B1 or OATP1B3, renal organic anion uptake transporters OAT1 and OAT3, or the organic cation uptake transporters OCT1 or OCT2 at clinically relevant concentrations. Therefore, clinical drug-drug interactions as a result of ceritinib-mediated inhibition of substrates for these transporters are unlikely to occur. (See Drug Interactions under 16 NON-CLINICAL TOXICOLOGY, DETAILED PHARMACOLOGY).

Gastric acid reducing agents

Ceritinib demonstrates pH-dependent solubility and becomes poorly soluble as pH increases *in vitro*. In a drug interaction study in healthy subjects (N=22), co-administration of a single dose of 750 mg of ceritinib fasted and esomeprazole (a proton pump inhibitor) at 40 mg daily for 6 days decreased the ceritinib AUC by 76% (90% CI: 66%, 83%) and C_{max} by 79% (90% CI: 70%, 86%). However, coadministration of a single 750 mg ceritinib dose fasted with proton pump inhibitors for 6 days in a subgroup of patients from Study X2101 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 ceritinib once daily dosing. When the concurrent use of a H2-receptor antagonist or an antacid with ceritinib is necessary, the H2 blocker should be administered 10 hours before or 2 hours after the ceritinib dose, and the antacid should be administered 2 hours before or 2 hours after the ceritinib dose.

Heart Rate-Lowering Drugs

Asymptomatic cases of bradycardia have been observed in patients treated with ZYKADIA. (See 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Monitoring and Laboratory Tests; 10 CLINICAL PHARMACOLOGY, 10.2 Pharmacodynamics, Cardiac Electrophysiology). Avoid using ZYKADIA in combination with other bradycardic agents (e.g., beta-blockers, digitalis glycosides, non-dihydropyridine calcium channel blockers, cholinesterase inhibitors, alpha2-adrenoceptor agonists, and sphingosine-1 phosphate receptor modulators).

QT Interval-Prolonging Drugs

The concomitant use of ZYKADIA with QT interval-prolonging drugs should be avoided to the extent possible (See 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Monitoring and Laboratory Tests; 10 CLINICAL PHARMACOLOGY, 10.2 Pharmacodynamics, Cardiac Electrophysiology). Drugs that have been associated with QT interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTc interval prolongation and/or torsade de pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide)

- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone)
- Class 1C antiarrhythmics (e.g., flecainide, propafenone)
- antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone)
- antidepressants (e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants [e.g., amitriptyline, imipramine, maprotiline])
- opioids (e.g., methadone)
- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, azithromycin, tacrolimus)
- quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin)
- pentamidine
- antimalarials (e.g., quinine, chloroquine)
- azole antifungals (e.g., ketoconazole, fluconazole, voriconazole)
- domperidone
- 5-hydroxytryptamine (5-HT)3 receptor antagonists (e.g., ondansetron)
- tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, lapatinib, vandetanib)
- arsenic trioxide
- histone deacetylase inhibitors (e.g., vorinostat)
- beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol)

Drugs that Affect Electrolytes

Caution should be observed if ZYKADIA is administered with drugs that can disrupt electrolyte levels. Drugs that can disrupt electrolyte levels include, but are not limited to, the following:

- loop, thiazide, and related diuretics
- laxatives and enemas
- amphotericin B
- high-dose corticosteroids

The above list of potentially interacting drugs is not comprehensive. Current information sources should be consulted for newly approved drugs that decrease heart rate, prolong the QT/QTc interval, or decrease electrolytes, as well as for older drugs for which these effects have recently been established.

9.2 Drug-Food Interactions

ZYKADIA should be taken with food. The bioavailability of ceritinib is increased in the presence of food.

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

9.3 Drug-Herb Interactions

St. John's Wort (Hypericum perforatum) is a potent CYP3A4 inducer. Co-administration with ZYKADIA may lead to increased ZYKADIA metabolism, therefore decreased ZYKADIA plasma concentrations (see 9.4 Drug-Drug Interactions).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Ceritinib is a highly selective and potent ALK kinase inhibitor. Ceritinib inhibits autophosphorylation of

ALK, ALK-mediated phosphorylation of downstream signaling protein STAT3, and proliferation of ALK-dependent cancer cells both in vitro and in vivo. Ceritinib also inhibits insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (INSR), and ROS1 (ROS1, c-ros) at clinically relevant doses.

Ceritinib was demonstrated effective against EML4-ALK and NPM-ALK kinase activity in a NSCLC and lymphoma cell line, resulting in inhibition of cell proliferation in vitro and regression of tumors in EML-ALK and NPM-ALK derived xenografts in mouse and rat.

A single-dose pharmacodynamic study and multiple-daily dose efficacy study performed in lymphoma and lung cancer tumor models indicated that a 60% to 80% reduction in the ALK signaling pathway may be required to achieve tumor regression.

10.2 Pharmacodynamics

Cardiac Electrophysiology:

The potential for QTc interval prolongation by ceritinib was assessed in Study X2101, an open-label, dose-escalation and expansion study investigating the safety, pharmacokinetics, and anti-tumor activity of ceritinib in patients with tumors confirmed to have genetic abnormalities in ALK. Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of ceritinib on the QT interval in patients treated with ZYKADIA 750 mg once daily fasted.

The mean change from baseline in ECG parameters in Study X2101 was 13.6 ms (90% CI: 11.73; 15.41) for the QTc interval, -9.2 bpm (90% CI: -10.58; -7.86) for heart rate, 3.7 ms (90% CI: 2.37; 5.10) for the PR interval, and 1.2 ms (90% CI: 0.45; 1.96) for the QRS duration in the 750 mg fasted dose arm (N=223) at steady-state pre-dose on Day 22. A central analysis of ECG data demonstrated no cases of QTc >500 msec in the 750 mg arm (N=255) under fasted conditions. There were 7 patients (2.8%) with a QTc increase from baseline >60 msec. A pharmacokinetic/pharmacodynamic analysis suggested that ceritinib causes concentration-dependent increases in QTc.

In Study A2303, the observed mean change from baseline QTc at pre-dose on Day 22 was 14.9 ms (90% CI: 12.2, 17.6) in 101 patients receiving ceritinib 750 mg once daily fasted. According to a PK/PD analysis based on data from 86 patients in Study A2303, the predicted change from baseline QTc at mean steady-state C_{min} was 14.1 ms (90% CI: 10.0, 18.2).

In Study A2303, a categorical outlier analysis of ECG data in 115 patients demonstrated new QTc >500 msec in 1 patient (0.9%) and increases from baseline >60 ms in 7 patients (6.1%). Adverse events of QT prolongation (primarily ECG QT prolonged) were reported for 13 patients (11.3%).

In Study A2301, the observed mean change from baseline QTc at pre-dose on Day 22 was 13.5 ms (90% CI: 11.8, 15.3) in 182 patients receiving ceritinib 750 mg once daily fasted. According to a PK/PD analysis based on data from 167 patients in Study A2301, the predicted change from baseline QTc at mean steady-state C_{min} was 11.7 ms (90% CI: 8.5, 14.9).

In Study A2301, a categorical outlier analysis of ECG data in 189 patients demonstrated new QTc >500 msec in 5 patients (2.6%) and increases from baseline >60 ms in 15 patients (7.9%). Adverse events of QT prolongation (primarily ECG QT prolonged) were reported for 21 patients (11.1%).

A pharmacokinetic/pharmacodynamic analysis suggested that ceritinib causes concentration-dependent increases in QTc (see 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS, 9 DRUG INTERACTIONS, 4 DOSAGE AND ADMINISTRATION).

10.3 Pharmacokinetics

Absorption

After single oral administration of ceritinib in patients, peak plasma levels (C_{max}) of ceritinib were achieved at approximately 4 to 6 hours, and the area under the curve (AUC) and C_{max} increased dose proportionally over 50 to 750 mg dose range under fasted conditions. The absolute bioavailability of ceritinib has not been determined. (See Table 17 under 16 NON-CLINICAL TOXICOLOGY,DETAILED PHARMACOLOGY).

Following ceritinib 750 mg once daily fasted 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 dose range under fasted conditions once daily.

Food effect

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 A2112 (ASCEND-8) in patients comparing ZYKADIA 450 mg or 600 mg daily with food (approximately 100 to 500 calories and 1.5 to 15 grams of fat) to 750 mg daily under fasted conditions, there was no clinically meaningful difference in the systemic steady-state exposure of ceritinib for the 450 mg with food arm (N=36) compared to the 750 mg fasted arm (N=31), with only small increases in steady-state AUC (90% CI) by 4% (-13%, 24%) and C_{max} (90% CI) by 3% (-14%, 22%). In contrast, the steady-state AUC (90% CI) and C_{max} (90% CI) for the 600 mg with food arm (N=30) increased by 24% (3%, 49%) and 25% (4%, 49%), respectively, compared to the 750 mg fasted arm. The maximum recommended dose of ZYKADIA is 450 mg taken orally once daily with food (see 4 DOSAGE AND ADMINISTRATION).

Distribution:

Binding of ceritinib to human plasma proteins *in vitro* is approximately 97% in a concentration independent manner, from 50 ng/mL to 10,000 ng/mL. Ceritinib also has a slight preferential distribution to red blood cells, relative to plasma, with a mean *in vitro* blood-to-plasma ratio of 1.35. The apparent volume of distribution (Vd/F) is 4230 L following a single 750 mg fasted dose of ZYKADIA in patients. *In vitro* studies suggest that ceritinib is a substrate for P-glycoprotein (P-gp), but not of breast cancer resistance protein (BCRP) or multi-resistance protein 2 (MRP2). The *in vitro* apparent passive permeability of ceritinib was determined to be low.

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

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 fasted radiolabeled ceritinib dose, ceritinib as the parent compound was the main circulating component (82%) in human plasma. A total of 11 metabolites were found circulating in plasma at low levels with mean contribution to the radioactivity

AUC of ≤2.3% for each metabolite. Main biotransformation pathways identified in healthy subjects included mono-oxygenation, O-dealkylation, and N-formylation. Secondary biotransformation pathways involving the primary biotransformation products included glucuronidation and dehydrogenation. Addition of a thiol group to O-dealkylated ceritinib was also observed.

Based on in vitro data, ceritinib may inhibit CYP3A and CYP2C9 at clinical concentrations. Time-dependent inhibition of CYP3A was also observed.

Elimination

Following a single 750 mg ceritinib dose under fasted conditions, the geometric mean apparent plasma terminal half-life ($t_{1/2}$) of ceritinib was 41 hours in patients. (See Table 17 under 16 NON-CLINICAL TOXICOLOGY, DETAILED PHARMACOLOGY). 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).

Following oral administration of a single 750 mg radiolabeled ceritinib dose under fasted conditions, 91% of the administered oral dose was recovered in the feces (with a mean 68% of an oral dose as unchanged parent compound) while 1.3% of the administered oral dose was recovered in the urine.

Special Populations and Conditions

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

- **Hepatic Insufficiency:** 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 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS, 7.1 Special populations). 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 Insufficiency:** 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 345 patients with mild renal impairment (CrCl 60 to <90 mL/min), 82 patients with moderate renal impairment (CrCl 30 to <60 mL/min) and 546 patients with normal renal function (≥90 mL/min), ceritinib exposures were similar in patients with mild and moderate renal impairment and normal renal function. Patients with severe renal impairment (CrCl <30 mL/min) were not included in the clinical trial.

11 STORAGE, STABILITY AND DISPOSAL

ZYKADIA (ceritinib) should not be stored above 30°C.

ZYKADIA capsules must be kept out of the reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

No special requirements

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

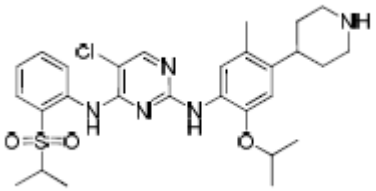
Drug Substance

Proper name: Ceritinib

Chemical name: 5-Chloro-2-N-{5-methyl-4-(piperidin-4-yl)-2-[(propan-2- sulfonyl) oxy]phenyl}-4-N-[2-(propane-2-sulfonyl)phenyl]pyrimidine-2,4-diamine

Molecular formula and molecular mass: C28H36ClN5O3S and 558.14

Structural formula:



Physicochemical properties:

Physical Description: White to almost white or light yellow or light brown powder.
Solubility: At 25°C, ceritinib drug substance has good solubility in very acidic aqueous medium. The solubility decreases significantly with increasing pH. A good solubility is found in the organic medium methanol.
pH: The pH of a 1% aqueous suspension of LDK378 in water is 6.86.
pKa: The pKa values for ceritinib are 9.7 and 4.1
Partition Coefficient/Distribution coefficient: The measured log P of ceritinib in octanol/water is 4.6. The log D of ceritinib in octanol/buffer pH 6.8 is 1.69
Melting point: The melting point is 174.0°C (as determined by Thermogravimetry-Differential Thermal Analysis [TGA-DTA])

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Previously Untreated ALK-Positive Locally Advanced or Metastatic NSCLC

NOC **Phase III study A2301**

The efficacy and safety of ZYKADIA for the treatment of locally advanced or metastatic ALK-positive NSCLC patients with and without brain metastasis, who have not received previous systemic treatment anti-cancer therapy (including ALK inhibitor) with the exception of neo-adjuvant or adjuvant therapy, was investigated in a global multicenter, randomized, open-label Phase 3 Study A2301 (ASCEND 4).

Patients with symptomatic central nervous system (CNS) metastases who were neurologically unstable or had required increasing doses of corticosteroids within the 2 weeks prior to screening to manage CNS symptoms were excluded from the study.

The primary efficacy endpoint was Progression-Free Survival (PFS), as determined by a Blinded Independent Review Committee (BIRC), according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The key secondary endpoint was Overall Survival (OS). Other secondary endpoints included Overall Response Rate (ORR), Duration of Response (DOR), determined by BIRC and by Investigators and patient reported outcomes (PROs).

Intracranial ORR (OIRR), intracranial DCR (IDCR) and duration of intracranial response (DOIR) determined by BIRC neuro-radiologist per modified RECIST 1.1 (i.e. up to 5 lesions in the brain) were used to assess the antitumor activity in the brain.

Patients were allowed to continue the assigned study treatment beyond initial progression in case of continued clinical benefit as per the Investigator's opinion. Patients randomized to the chemotherapy arm could crossover to receive ceritinib upon RECIST-defined disease progression by BIRC.

A total of 376 patients were randomized in a 1:1 ratio (stratified by WHO performance status, prior adjuvant/neoadjuvant chemotherapy and presence/absence of brain metastasis at screening) to receive either ceritinib (750 mg daily, fasted) or chemotherapy (based on Investigator's choice - pemetrexed [500 mg/m^2] plus cisplatin [75 mg/m^2] or carboplatin [AUC 5-6], administered every 21 days for 4 cycles. Patients who completed 4 cycles of chemotherapy (induction) without progressive disease subsequently received pemetrexed (500 mg/m^2) as single-agent maintenance therapy every 21 days. One hundred and eighty-nine (189) patients were randomized to ceritinib and one hundred eighty-seven (187) were randomized to chemotherapy.

Baseline disease characteristics were balanced between the two treatment arms as shown in Table 9.

Table 9 Demographics and Disease Characteristics in Study A2301

Characteristics	**Ceritinib 750 mg fasted N=189 n (%)**	**Chemotherapy N=187 n (%)**
Sex, n (%)		
Male	87 (46.0)	73 (39.0)
Female	102 (54.0)	114 (61.0)
Age (years), n (%)		
Median (range)	55.0 (22-81)	54.0 (22-80)
<65 years	143 (75.7)	152 (81.3)
≥65 years	46 (24.3)	35 (18.7)

Characteristics	Ceritinib 750 mg fasted N=189 n (%)	Chemotherapy N=187 n (%)
Race, n (%)		
Caucasian	104 (55.0)	98 (52.4)
Black	3 (1.6)	3 (1.6)
Asian	76 (40.2)	82 (43.9)
Native American	3 (1.6)	2 (1.1)
Other	3 (1.6)	2 (1.1)
WHO/ECOG Performance Status at baseline, n (%)		
0	69 (36.5)	70 (37.4)
1	107 (56.6)	105 (56.1)
2	13 (6.9)	11 (5.9)
Missing	0	1 (0.5)
Smoking status, n (%)		
Never smoked	108 (57.1)	122 (65.2)
Former smoker	66 (34.9)	50 (26.7)
Current smoker	15 (7.9)	15 (8.0)
Disease Stage, n (%)		
Locally advanced	9 (4.8%)	5 (2.7%)
Metastatic	180 (95.2%)	182 (97.3%)
Histological classification, n (%)		
Adenocarcinoma	180 (95.2)	183 (97.9)
Adenosquamous cell carcinoma	2 (1.1)	2 (1.1)
Large cell carcinoma	3 (1.6)	1 (0.5)
Undifferentiated carcinoma	1 (0.5)	0
Other	3 (1.6)	1 (0.5)
Brain Metastases, n (%)		
Present	59 (31.2)	62 (33.2)
Absent	130 (68.8)	125 (66.8)

The median duration of follow-up was 19.7 months (from randomization to data cut-off date).

Previously Treated ALK-positive Locally Advanced or Metastatic NSCLC

NOC/c **Phase I Study X2101**

The use of ZYKADIA (ceritinib) in the treatment of patients with ALK-positive NSCLC was investigated in a multicenter, open-label study (X2101) which included a dose-escalation phase and an expansion phase at a fasted dose of 750 mg. All patients enrolled in the registration study had locally advanced or metastatic malignancy that had progressed despite standard therapy and all patients were previously tested for ALK rearrangement. Patients with controlled or asymptomatic brain metastases were eligible for the study. Prior ALK inhibitor therapy was permitted. Two-hundred and ninety of the 304 patients enrolled in the study were ALK-positive NSCLC patients. At the time of the data cut-off, a total of 246

ALK-positive NSCLC patients were enrolled who were treated at a ZYKADIA dose of 750 mg once daily fasted: 163 who had received prior treatment with crizotinib (Full Analysis Set).
Of the 163 patients who were treated with a prior ALK inhibitor (all treated with crizotinib) with an available report, ALK positivity was confirmed in 162 patients (99.4%): by FISH in 157 patients (96.3%), by RT-PCR in 3 patients (1.8%), by IHC in 1 patient (0.6%), and by other method in 1 patient (0.6%).

The primary evaluation was based on overall response rate (ORR) and duration of response (DOR) by Investigator assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 for patients who were treated with a ZYKADIA dose of 750 mg fasted. An additional evaluation of ORR and DOR was also performed based on a central Blinded Independent Review Committee (BIRC) assessment according to RECIST 1.0. Demographic and disease characteristics for the study are provided in Table 10.

Table 10 Demographics and Disease Characteristics in Study X2101

Characteristics	**NSCLC patients treated with 750 mg/day fasted N=163**
Sex, n (%)	
Male	75 (46)
Female	88 (54)
Age (years), n (%)	
Median (range)	52 (24-80)
<65 years	141 (86.5)
≥65 years	22 (13.5)
Race, n (%)	
Caucasian	108 (66.3)
Black	4 (2.5)
Asian	47 (28.8)
Native Islander	1 (0.6)
Other	3 (1.8)
WHO/ECOG Performance Status at baseline, n (%)	
0	38 (23.3)
1	104 (63.8)
2	20 (12.3)
3	1 (0.6)
Smoking status, n (%)	
Never smoked	109 (66.9)
Former smoker	49 (30.1)
Current smoker	5 (3.1)
Disease Stage, n (%)	
Locally advanced	3 (1.8)
Metastatic	157 (96.3)
Data missing	3 (1.8)
Histological classification, n (%)	
Adenocarcinoma	152 (93.3)
Large cell carcinoma	2 (1.2)
Squamous cell carcinoma	3 (1.8)
Adenosquamous cell carcinoma	2 (1.2)
Other	2 (1.2)

Characteristics	NSCLC patients treated with 750 mg/day fasted N=163
Missing	2 (1.2)
Number of prior antineoplastic regimens, n (%)	
1	26 (16.0)
2	45 (27.6)
3	35 (21.5)
>3	57 (35.0)

NOC/c **Phase III Study A2303**

The efficacy and safety of ZYKADIA for the treatment of locally advanced or metastatic ALK-positive NSCLC adult patients with and without brain metastasis, who have received previous treatment with crizotinib, was demonstrated versus standard chemotherapy (pemetrexed/docetaxel) in a global multicenter, randomized, open-label Phase III Study A2303 (ASCEND 5).

The primary efficacy endpoint was Progression-Free Survival (PFS), as determined by a Blinded independent review committee (BIRC), according to RECIST 1.1. The key secondary endpoint was Overall Survival (OS). Other secondary endpoints included Overall Response Rate (ORR), Duration of Response (DOR), disease control rate (DCR), and time to response (TTR) determined by BIRC and by Investigator, PFS by Investigator and patient reported outcomes (PROs), including disease-related symptoms, functioning, and health-related quality of life.

Intracranial ORR (OIRR), intracranial DCR (IDCR) and duration of intracranial response (DOIR) determined by BIRC neuro-radiologist per modified RECIST 1.1 (i.e. up to 5 lesions in the brain) were used to assess the antitumor activity in the brain.

Patients were allowed to continue the assigned study treatment beyond initial progression in case of continued clinical benefit as per the Investigator's opinion. Patients randomized to the chemotherapy arm could crossover to receive ceritinib upon RECIST-defined disease progression confirmed by BIRC.

A total of 231 patients with advanced ALK positive NSCLC who have received prior treatment with crizotinib and chemotherapy (one or two regimen including a platinum-based doublet) were included in the analysis. 115 patients were randomized to ceritinib and 116 were randomized to chemotherapy (either pemetrexed or docetaxel). 73 patients received docetaxel and 40 received pemetrexed. In the ceritinib arm, 115 patients were treated with 750 mg once daily fasted.

Baseline disease characteristics were well-balanced between the two treatment arms as shown in Table 11.

Table 11 Demographics and Disease Characteristics in Study A2303

Characteristics	Ceritinib 750 mg fasted N=115 n (%)	Chemotherapy N=116 n (%)
Sex, n (%)		
Male	47 (40.9)	55 (47.4)
Female	68 (59.1)	61 (52.6)
Age (years), n (%)		
Median (range)	54.0 (30-77)	54.0 (28-84)
<65 years	89 (77.4)	89 (76.7)
≥65 years	26 (22.6)	27 (23.3)
Race, n (%)	81 (70.4)	68 (58.6)
Caucasian	0	1 (0.9)
Black	30 (26.1)	38 (32.8)
Asian	2 (1.7)	5 (4.3)
Unknown	2 (1.7)	4 (3.4)
Other		
WHO/ECOG Performance Status at		
baseline, n (%)	56 (48.7)	51 (44.0)
0	50 (43.5)	60 (51.7)
1	9 (7.8)	5 (4.3)
2		
Smoking status, n (%)		
Never smoked	71 (61.7)	61 (52.6)
Former smoker	39 (33.9)	51 (44.0)
Current smoker	4 (3.5)	1 (0.9)
Missing	1 (0.9)	3 (2.6)
Disease Stage, n (%)		
Locally advanced	1 (0.9)	1 (0.9)
Metastatic	114 (99.1)	115 (99.1)
Histological classification, n (%)		
Adenocarcinoma	111 (96.5)	113 (97.4)
Squamous cell carcinoma	0	2 (1.7)
Undifferentiated carcinoma	3 (2.6)	1 (0.9)
Other	1 (0.9)	0
Brain Metastases, n (%)		
Present	65 (56.5)	69 (59.5)
Absent	50 (43.5)	47 (40.5)

All patients were treated with prior crizotinib. 198 patients (81.8%) received crizotinib as last treatment (81.7% in the ceritinib arm, 81.9% in the chemotherapy arm). All except one patient received prior chemotherapy (including a platinum doublet) for advanced disease; 11.3% of the patients in the ceritinib arm and 12.1% of the patients in the chemotherapy arm were treated with two prior chemotherapy regimen for advanced disease.

The median duration of follow-up was 16.5 months (from randomization to data cut-off date).

14.2 Study Results

Previously Untreated ALK-Positive Locally Advanced or Metastatic NSCLC

NOC **Phase III study A2301**

The study met its primary objective demonstrating a statistically significant and clinically meaningful improvement in PFS by BIRC with an estimated 45% risk reduction in the ceritinib arm compared to the chemotherapy arm (HR: 0.55 with 95% CI: 0.42, 0.73, p<0.001). The median PFS was 16.6 months (95% CI: 12.6, 27.2) and 8.1 months (95% CI: 5.8, 11.1) for the ceritinib arm and chemotherapy arm, respectively (see Table 9 and Figure 1).

The PFS results by Investigator assessment and in subgroups including age, gender, race, smoking class, Eastern Cooperative Oncology Group (ECOG) performance status and disease burden were generally consistent.

The overall survival (OS) data was not mature with 107 deaths (48 [25.4%] and 59 [31.6%] in the ceritinib and chemotherapy arms, respectively) representing approximately 42.3% of the required events for the final OS analysis. The median OS was not estimable in the ceritinib arm and was 26.2 months (95% CI: 22.8, NE) in the chemotherapy arm (HR: 0.73 with 95% CI: 0.50, 1.08, stratified log-rank test one-sided p=0.056). The estimated OS rate (95% CI) at 24 months was 70.6% (62.2, 77.5) and 58.2% (47.6, 67.5) for ceritinib arm and chemotherapy arm, respectively. Eighty-one patients (43.3%) in the chemotherapy arm received subsequent ceritinib as the first subsequent antineoplastic therapy after study treatment discontinuation.

Efficacy data from Study A2301 are summarized in Table 12, and the Kaplan-Meier plot for PFS is shown in Figure 1.

Table 12 Efficacy results in patients with previously untreated ALK-positive locally advanced or metastatic NSCLC in Study A2301

	Ceritinib (N=189)	Chemotherapy (N=187)
Progression-Free Survival (based on BIRC)		
Number of events, n (%)	89 (47.1)	113 (60.4)
Median, months[d] (95% CI)	16.6 (12.6, 27.2)	8.1 (5.8, 11.1)
HR (95% CI)[a]	0.55 (0.42, 0.73)	
p-value[b]	<0.001	
Overall Survival[c]		
Number of events, n (%)	48 (25.4)	59 (31.6)
Median, months[d] (95% CI)	NE (29.3, NE)	26.2 (22.8, NE)
OS rate at 24 months[d], % (95% CI)	70.6 (62.2, 77.5)	58.2 (47.6, 67.5)
HR (95% CI)[a]	0.73 (0.50,1.08)	
p-value[b]	0.056	
Tumor Response (based on BIRC)		
Objective response rate (95% CI)	72.5% (65.5, 78.7)	26.7% (20.5, 33.7)
Duration of response (based on BIRC)		
Number of responders	137	50
Median, months[d] (95% CI)	23.9 (16.6, NE)	11.1 (7.8, 16.4)
Event-free rate at 18 months[d], % (95% CI)	59.0 (49.3, 67.4)	30.4 (14.1, 48.6)

HR=hazard ratio; CI=confidence interval; BIRC=Blinded Independent Review Committee; NR=not reached; CR=complete response; PR=partial response

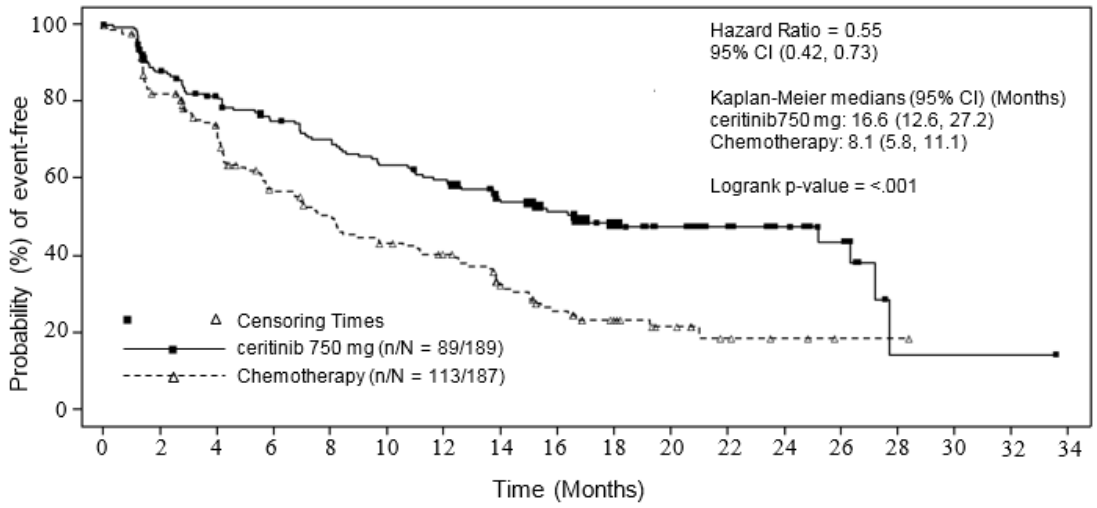
[a] Based on the Cox proportional hazards stratified analysis.

[b] Based on the stratified log-rank test.

[c] OS was not adjusted for the effects of cross over at this interim analysis.

[d] Estimated using the Kaplan-Meier method.

Figure 1 **Kaplan-Meier plot of progression-free survival as assessed by BIRC in Study A2301 (FAS)**



	No. of patients still at risk																	
Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
Ceritinib 750 mg	189	155	139	125	116	105	98	76	59	43	32	23	16	11	1	1	1	0
Chemotherapy	187	136	114	82	71	60	53	35	24	16	11	5	3	1	1	0	0	0

Analyses of patient-reported outcome (PRO) measures suggested a delay in time to deterioration for lung cancer specific symptoms (composite endpoint of cough, pain and dyspnea based on Lung Cancer Symptom Score [LCSS] questionnaire: HR 0.61; 95% CI: 0.41, 0.90) in patients treated with ceritinib compared to chemotherapy. Patients in the ceritinib arm (750 mg daily, fasted) appeared to have reported more intense diarrhea experience (difference between ceritinib and chemotherapy arms in change of diarrhea score [least square means] from baseline: 22.1; 95% CI: 19.5, 24.7 based on EORTC QLQ-C30 questionnaire). These PRO results should be interpreted with caution, as patients were not blinded to treatment assignment.

In Study A2301, 44 out of 121 patients had measurable brain metastasis at baseline and at least one post-baseline brain radiological assessment (22 in the ceritinib arm and 22 patients in the chemotherapy arm). Intracranial ORR based on BIRC assessment were 72.7% (95% CI: 49.8, 89.3) and 27.3% (95% CI: 10.7, 50.2) in the ceritinib and chemotherapy arms, respectively. Among these patients with measurable brain metastasis at baseline and at least one post-baseline, 59.1% (13/22) in the ceritinib arm and 81.8% (18/22) in the chemotherapy arm did not receive prior radiotherapy to the brain. PFS results in patients with and without CNS metastases (measurable or non-measurable) at baseline based on BIRC assessment are summarized in Table 13.

Table 13 **PFS with and without brain metastases in Study A2301 by BIRC assessment**

	BIRC	
	Ceritinib	**Chemotherapy**
With Brain Metastases	**N=59**	**N=62**
Progression Free Survival		
Median, months (95% CI)	10.7 (8.1, 16.4)	6.7 (4.1, 10.6)

	BIRC	
	Ceritinib	**Chemotherapy**
HR (95% CI)	0.70 (0.44, 1.12)	
Without Brain Metastases	**N=130**	**N=125**
Progression Free Survival		
Median, months (95% CI)	26.3 (15.4, 27.7)	8.3 (6.0, 13.7)
HR (95% CI)	0.48 (0.33, 0.69)	

Previously Treated ALK-positive Locally Advanced or Metastatic NSCLC

NOC/c **Phase I Study X2101**

Of the 163 ALK-positive NSCLC patients treated at a dose of 750 mg fasted, 89 (54.6%; 95% CI: 46.6, 62.4) patients by Investigator assessment and 71 (43.6%; 95% CI: 35.8, 51.5) by BIRC assessment had a tumor response that was confirmed at least 4 weeks after the initial assessment (Table 14). The median time to the first objective tumor response (complete response [CR] or partial response [PR]) that was subsequently confirmed was 6.1 weeks both by Investigator and BIRC assessment. The median DOR in patients who responded was 7.4 months (95% CI: 5.4, 10.1) by Investigator assessment and 7.1 months (95% CI: 5.6, Not estimable) by BIRC assessment.

Table 14 **Locally advanced or metastatic ALK-positive NSCLC efficacy results for the 750 mg fasted treatment dose arm who received prior crizotinib treatment (FAS) in Study X2101**

Efficacy Parameter	**Investigator assessment**	**BIRC assessment**
	(N=163)	**(N=163)**
Overall Response Rate (CR+PR)[a], [(%) (95% CI)]	54.6% (46.6, 62.4)	43.6% (35.8, 51.5)
CR, (%)	1.2%	2.5%
PR, (%)	53.4%	41.1%
Duration of Response [Median (95% CI)]	7.4 months (5.4, 10.1)	7.1 months (5.6, NE[b])

[a] CR (complete response), PR (partial response) confirmed

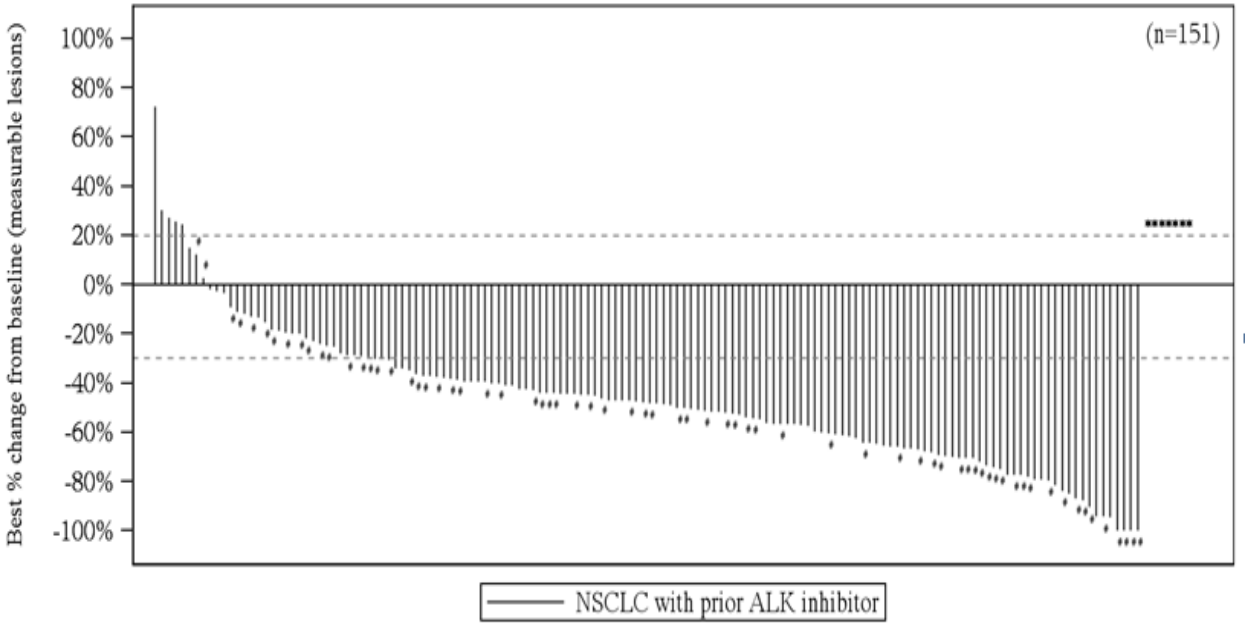
BIRC = blinded independent review committee

ORR and DOR assessed by RECIST 1.0

[b] NE = Not estimable

Post-baseline tumor measurements were available for 151 patients with measurable disease at baseline and at least 1 valid post-baseline assessment without an unknown response for overall or target lesions out of the 163 patients. A waterfall plot displaying the maximum decrease from baseline in the sum of the longest tumor diameters shows that the majority of patients treated with ZYKADIA had a reduction in tumor burden (Figure 2).

Figure 2 Waterfall Plot of Best Percent Change in Target Lesions from Baseline by Patient Based on Investigator Assessment (ALK-Positive NSCLC) in Study X2101



Best percentage change from baseline<0 90.07% (136)
Best percentage change from baseline>0 5.30% (8)
*% change in target lesion available but contradicted by overall lesion response = PD (contradicting assessment represents the only valid post-baseline assessment) 4.64% (7)
n (number of patients with measurable disease at baseline and at least one valid post-baseline assessment) is used for calculation of percentages.
A post-baseline assessment with unknown response for target lesion or unknown overall lesion response is considered invalid.
PFS event.

NOC/c **Phase III Study A2303**

The study met its primary objective demonstrating a statistically significant and clinically meaningful improvement in PFS by BIRC with an estimated 51% risk reduction in the ceritinib arm compared to chemotherapy arm (HR: 0.49 with 95% CI: 0.36, 0.67). The median PFS was 5.4 months (95% CI: 4.1, 6.9) and 1.6 months (95% CI: 1.4, 2.8) for the ceritinib arm and chemotherapy arm, respectively (see Table 15 and Figure 3).

The PFS benefit of ceritinib was robust and consistent by Investigator assessment and across various subgroups including age, gender, race, smoking class, ECOG performance status, and presence of brain metastases or prior response to crizotinib.

The benefit was further supported analysis of ORR and DCR. Ceritinib also significantly improved BIRC-assessed ORR as compared to chemotherapy with durable response (see Table 15).

As pre-specified in the protocol, OS was formally tested as the primary efficacy endpoint PFS by BIRC assessment was statistically significant and favoring the ceritinib arm. OS data was not mature with 48 (41.7%) events in the ceritinib arm and 50 (43.1%) events in the chemotherapy arm, corresponding to approximately 50% of the required events for final OS. In addition, 81 patients (69.8%) in the

chemotherapy arm received subsequent ceritinib as first antineoplastic therapy after study treatment discontinuation.

Efficacy data from Study A2303 are summarized in Table 15, and the Kaplan-Meier curve for PFS is shown in Figure 3.

Table 15 Efficacy results in patients with previously treated ALK-positive locally advanced or metastatic NSCLC in Study A2303

	Ceritinib (N=115)	Chemotherapy (N=116)
Progression-free survival (based on BIRC)		
Number of events, n (%)	83 (72.2%)	89 (76.7%)
Median, months (95% CI)	5.4 (4.1, 6.9)	1.6 (1.4, 2.8)
HR (95% CI)[a]	0.49 (0.36, 0.67)	
p-value[b]	<0.001	
Tumor response (based on BIRC)		
Objective response rate (95% CI)	39.1% (30.2, 48.7)	6.9% (3.0, 13.1)
Duration of response		
Number of responders	45	8
Median, months[c] (95% CI)	6.9 (5.4, 8.9)	8.3 (3.5, NE)
Event-free probability estimate at 9 months[c] (95% CI)	31.5% (16.7%, 47.3%)	45.7% (6.9%, 79.5%)

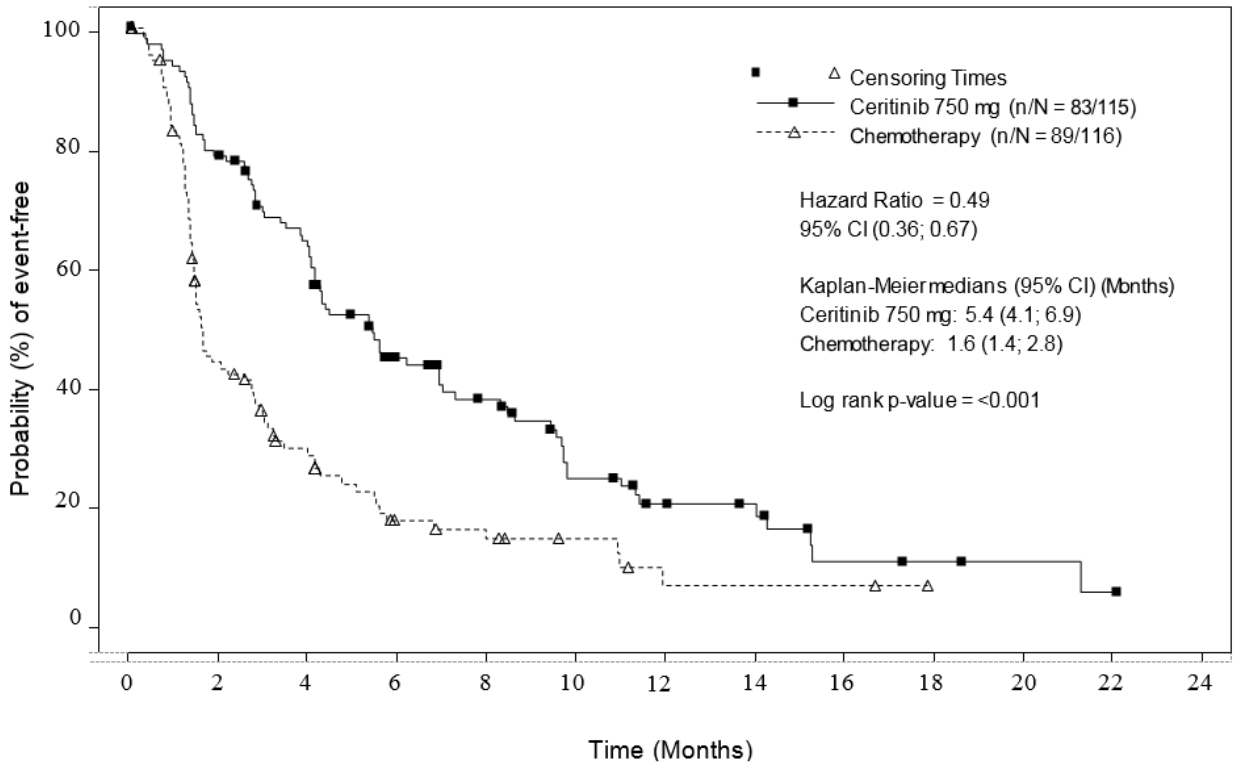
HR=hazard ratio; CI=confidence interval; BIRC=Blinded Independent Review Committee; NE=not estimable;

[a] Based on the Cox proportional hazards stratified analysis.

[b] Based on the stratified log-rank test.

[c] Estimated using the Kaplan-Meier method.

Figure 3 Kaplan-Meier plot of progression-free survival as assessed by BIRC in Study A2303 (FAS)



	No. of patients still at risk												
Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24
Ceritinib 750 mg	115	87	68	40	31	18	12	9	4	3	2	1	0
Chemotherapy	116	45	26	12	9	6	2	2	2	0	0	0	0

Patient reported outcome questionnaires were completed by 75% or more of patients in the ceritinib and chemotherapy arms for all questionnaires at most of the time points during the course of the study.

Significant improvements were reported for the majority of lung cancer specific symptoms for ZYKADIA versus chemotherapy (LCSS and QLQ-LC13 scores). Time to deterioration for cough, pain and dyspnea was significantly prolonged for the individual scales (p-value<0.05) or when combined into a composite score (p-value <0.001) in the LCSS and LC13 instruments. Median time to definitive deterioration for the LCSS composite endpoint (pain, cough, shortness of breath) was 18 months (95% CI: 13.4, NE) in the ceritinib arm versus 4.4 months (95% CI: 1.6, 8.6) in the chemotherapy arm. Median time to definitive deterioration for the same endpoint in the LC13 instrument was 11.1 months (95% CI 7.1, 14.2) in the ceritinib arm versus 2.1 months (95% CI: 1.0, 5.6) in the chemotherapy arm.

The EQ-5D questionnaire showed a significant overall health status improvement for ZYKADIA in comparison to the chemotherapy.

In Study A2303, 133 patients with baseline brain metastasis (66 patients in the ceritinib arm and 67 patients in the chemotherapy arm) were assessed for intracranial response by BIRC neuro-radiologist. The intracranial ORR (OIRR) in patients with measurable disease in the brain at baseline and at least one post-baseline assessment was higher with ceritinib (35.3%, 95% CI: 14.2, 61.7) compared to chemotherapy (5.0%, 95% CI: 0.1, 24.9).
The median PFS by BIRC and Investigator using RECIST 1.1 was longer in the ceritinib arm compared to the chemotherapy arm in both subgroups of patients with brain metastases and without brain metastases (based on the extent of cancer CRF, see Table 16).

Table 16 PFS with and without brain metastases in Study A2303

	BIRC		Investigator	
	Ceritinib	**Chemotherapy**	**Ceritinib**	**Chemotherapy**
With Brain Metastases	**N=65**	**N=69**	**N=65**	**N=69**
Progression Free Survival				
Median, months (95% CI)	4.4 (3.4, 6.2)	1.5 (1.3, 1.8)	5.4 (3.9, 7.0)	1.5 (1.3, 2.1)
HR (95% CI)	0.54 (0.36, 0.80)		0.45 (0.31, 0.66)	
Without Brain Metastases	**N=50**	**N=47**	**N=50**	**N=47**
Progression Free Survival				
Median, months (95% CI)	8.3 (4.1, 14.0)	2.8 (1.4, 4.1)	8.3 (5.6, 13.4)	2.6 (1.4, 4.2)
HR (95% CI)	0.41 (0.24, 0.69)		0.32 (0.19, 0.54)	

Dose optimization Study A2112 (ASCEND-8)

The pharmacokinetics, safety, and efficacy of ZYKADIA 450 mg with food were evaluated in a dose optimization Study A2112 (ASCEND-8). A key secondary efficacy endpoint was overall response rate (ORR) according to RECIST 1.1 as evaluated by a Blinded Independent Review Committee (BIRC). The ORR in previously untreated ALK-positive NSCLC was consistent between the ZYKADIA 450 mg once daily with food (N=73) and ZYKADIA 750 mg once daily under fasted conditions (N=74) arms, 78.1% (95% CI: 66.9, 86.9) and 75.7% (95% CI: 64.3, 84.9), respectively.

15 MICROBIOLOGY

N/A

16 NON-CLINICAL TOXICOLOGY

DETAILED PHARMACOLOGY

Clinical Pharmacokinetics

Table 17 Descriptive Summary of Plasma Ceritinib Pharmacokinetic Parameters Following Single 750 mg Fasted Dose of Ceritinib and Multiple 750 mg Fasted Daily Dosing of Ceritinib

Parameters, Units	Dose Escalation	Expansion	
	Single-dose*	***Cycle 1 Day 1***	***Cycle 2 Day 1***
T_{max}, hr	6.02 (3.95-23.8)	6.00 (1.13-24.0)	6.00 (0-22.6)
	n=10	n=208	n=133
C_{max}, ng/mL	186 (127)	203 (101)	1010 (44.8)
	n=10	n=208	n=133
C_{trough}, hr	NA	NA	828 (48.4)
	NA	NA	n=169
AUC_{0-24h}, ng*hr/mL	3390 (121)	3340 (112)	22600 (37.1)
	n=10	n=73	n=23
AUC_{last}, ng*hr/mL	7870 (127)	2040 (175)	8900 (76.1)
	n=10	n=208	n=133
CL/F, L/hr	88.5 (163)	NA	33.2 (37.1)
	n=3		n=23
$t_{1/2}$, hr	40.6 (34.7)	NA	NA
	n=9		

Abbreviations: NA=not applicable; n=number of patients with non-missing values; AUC_{0-24h}=area under the plasma concentration-time curve from zero to 24 hr post-dose; AUC_{last}=area under the plasma concentration-time curve calculated to the last quantifiable concentration point; C_{trough}=trough (predose) concentration; C_{max}=maximum concentration; CL/F=apparent plasma clearance; $t_{1/2}$=elimination half-life; T_{max}=time to maximum plasma concentration

*Dose escalation part of the study included a 3-day single-dose PK run-in period to fully characterize the PK of ceritinib, followed by a period of daily dosing in continuous 21-day treatment cycles.

Values are median (range) for Tmax, geometric mean (CV% of geometric mean) for all others.

Drug Interactions

Potential to inhibit CYP enzymes

Based on *in vitro* data, ceritinib competitively inhibits the metabolism of a CYP3A substrate, midazolam, and a CYP2C9 substrate, diclofenac. Time-dependent inhibition of CYP3A was also observed. Co-administration of a single dose of midazolam (a sensitive CYP3A substrate) following 3 weeks of ZYKADIA dosing in patients (750 mg daily fasted) increased the midazolam AUC_{inf} (90% CI) by 5.4-fold (4.6, 6.3) compared to midazolam alone. Avoid co-administration of ceritinib with substrates primarily metabolized by CYP3A or CYP3A substrates known to have narrow therapeutic indices (e.g., cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, tacrolimus, alfentanil, and sirolimus). If unavoidable, consider dose reduction for co-administered medicines that are CYP3A substrates with narrow therapeutic indices.

Co-administration of a single dose of warfarin (a CYP2C9 substrate) following 3 weeks of ZYKADIA dosing in patients (750 mg daily fasted) increased the S-warfarin AUC_{inf} (90% CI) by 54% (36%, 75%) compared to warfarin alone. Avoid co-administration of ZYKADIA with substrates primarily metabolized by CYP2C9 or CYP2C9 substrates known to have narrow therapeutic indices (e.g., phenytoin and warfarin). If unavoidable, consider dose reduction for co-administered medicines that are CYP2C9 substrates with narrow therapeutic indices. Increase the frequency of international normalized ratio (INR) monitoring if co-administration with warfarin is unavoidable as the anti-coagulant effect of warfarin may be enhanced.

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

Based on *in vitro* studies, clinical drug-drug interactions are unlikely to occur as a result of ceritinib-mediated inhibition of the metabolism of drugs that are substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C19, and CYP2D6.

Potential to induce CYP enzymes

Enzyme induction studies in primary human hepatocytes indicate that there is a potential for ceritinib to be an inducer of CYP3A in vivo. However, due to the concomitant time-dependent inhibition of CYP3A and observed decrease in CL/F of ceritinib after multiple dosing relative to a single dose in Study X2101, it is unlikely that ceritinib would act as a CYP3A inducer clinically.

Potential to inhibit/induce P-gp

Based on *in vitro* data, ceritinib does not inhibit P-gp. Therefore, clinical drug-drug interactions as a result of ceritinib-mediated inhibition of substrates for P-gp are unlikely to occur.

Potential to inhibit hepatic uptake transporters

Based on *in vitro* data, ceritinib does not inhibit hepatic uptake transporters OATP1B1 and OATP1B3 at clinical concentrations.

Potential to inhibit renal uptake transporters

Based on *in vitro* data, ceritinib does not inhibit renal organic anion uptake transporters OAT1 and OAT3, or organic cation uptake transporters OCT1 and OCT2 at clinical concentrations.

Non-Clinical Pharmacokinetics

Plasma clearance of ceritinib (14% - 45% of hepatic blood flow) following an intravenous dose was moderate in the mouse (1.60 L/h/kg), rat (1.49 L/h/kg), and dog (0.552 L/h/kg), and low to moderate in the monkey (0.366-0.78 L/h/kg). The steady-state volume of distribution of ceritinib was high in the mouse, rat, dog, and monkey (6.5 - 20 L/kg). The terminal half-life of ceritinib was long in the mouse, rat, dog, and monkey (6.2 - 29 hours). Ceritinib was moderately absorbed after oral dosing in the rat and monkey (≥35%). Bioavailability was moderate in the mouse, rat, and monkey (~40-60%). There was no apparent gender difference in the exposure for monkeys and rats. No conclusive evidence of accumulation for rats was observed, while the monkey showed moderate accumulation (up to 2.7-fold on day 73). The plasma protein binding was high (94.6 – 98.5%) in the rat, dog, and monkey. Ceritinib and/or its metabolites in rat tissues were mainly distributed to the intestinal wall, uveal tract, pituitary gland, bile, adrenal cortex, Harderian gland, liver, spleen, lymph node, lung, kidney, thyroid, bone marrow, adrenal medulla, pancreas, thymus and salivary gland. Ceritinib and/or its metabolites displayed moderate testis penetration. Retention in melanin-rich tissues (uveal tract) was significant. Although the brain/blood concentration ratio of drug-related radioactivity was low compared to other tissues, it was higher than the 3% background associated with brain vasculature at all monitored time points. This indicates that drug-related radioactivity crossed the blood-brain barrier. Following a single oral dose of [^{14}C]ceritinib to the rat and monkey, unchanged ceritinib was the most abundant circulating drug-related compound found in the plasma of both species (84% - 100% of the total drug-related AUC). In rat plasma, it was the only drug-related compound found. Of the metabolites found in monkey plasma, none were present at mean levels > 3.6% of the total drug-related AUC. Following an oral dose of [^{14}C]ceritinib to either the rat or monkey, excretion of radioactivity was primarily through the fecal route

(> 90% of the radioactivity dose) with only a minor contribution from the urinary route (< 1% of the radioactivity dose). Unchanged ceritinib was also the most abundant drug-related compound found in the feces of the rat and monkey (60% - 80% of the administered dose).

Non-Clinical Pharmacology

Ceritinib is a selective and potent ALK kinase inhibitor that inhibits ALK-driven phosphorylation of protein STAT3, cell proliferation and survival of ALK-dependent cancer cells both *in vitro* and *in vivo*.

Primary Pharmacodynamics

In vitro

Ceritinib inhibited ALK kinase with an IC_{50} of 0.15 nM in the ALK biochemical assay. In a kinase panel of 36 enzymes, ceritinib inhibited only 2 other kinases, IGF-1R (IC_{50} = 8 nM) and INSR IC_{50} = 7 nM), with approximately 50-fold less potency than for ALK inhibition. Its activity for all other kinases in the panel was 500-fold less potent when compared with ALK. Ceritinib exhibited a concentration-dependent inhibitory effect on the ALK signaling pathway and demonstrated potent and selective growth inhibitory activity in human tumor cell lines carrying ALK translocations (EML4-ALK or NPM-ALK) or ALK gene amplification. In Ba/F3 cells that were engineered to express and to depend on activated ALK kinase (EML4-ALK) or ROS1 kinase (TEL-ROS1), ceritinib inhibited ALK-dependent and ROS1-dependent proliferation of Ba/F3 cells, with an IC_{50} of 27 nM and 180 nM, respectively.

In vivo

Ceritinib demonstrated anti-tumor activity in xenograft tumor models derived from NPM-ALK-positive ALCL cell Karpas299 or EML4-ALK-positive NSCLC cell NCI-H2228, causing complete or nearly complete tumor regression at 25 mg/kg/day orally (po) in mice and in rats. It exhibited dose- and concentration-dependent inhibition of the ALK signaling pathway *in vivo*, suggesting that a 60% to 80% reduction in the ALK signaling pathway may be required to achieve tumor regression. To assess ceritinib's activity towards IGF-1R *in vivo*, the NIH3T3:IGF-1R:IGF-2 mechanistic pharmacodynamic (PD) model was used. This model utilizes NIH3T3 cells that were engineered to express IGF-1R and its ligand, IGF-2, leading to the constant activation of the IGF-1R pathway through an autocrine loop. Ceritinib did not suppress IGF-1R pathway up to 100 mg/kg. Moreover, ceritinib has shown strong anti-tumor activity in the xenograft tumor model derived from a patient who progressed on crizotinib as well as in several non-clinical NCI-H2228 xenograft tumor models that had developed resistance to crizotinib.

The key *in vitro* and *in vivo* pharmacological data are summarized in Table 18 below.

Table 18 Summary of Selected Key Ceritinib Pharmacological Properties

Assay	Ceritinib IC_{50} (nM)	Ceritinib Dose (mg/kg)
Biochemical activity *in vitro*		
ALK enzyme	0.15	
IGF-1R enzyme	8	
INSR enzyme	7	
Cellular activity *in vitro*		
NCI-H2228 (EML4-ALK$^+$, NSCLC)	11	
Karpas299 (NPM-ALK$^+$, ALCL)	45	
NB-1 (ALK gene amplification, neuroblastoma)	24	
Ba/F3-EML4-ALK	27	

Ba/F3-TEL-ROS1	180	
Tumor regression *in vivo* (mouse)		
NCI-H2228 xenograft tumor model		25 mg/kg/day
Karps299 xenograft tumor model		25 mg/kg/day
Inhibition of signaling pathways *in vivo* (mouse)		
ALK pathway in NCI-H2228 tumor model		60-80% inhibition at 25 mg/kg/day
IGF-1R pathway in IGF-1R PD model		No inhibition at 100 mg/kg/day

Secondary Pharmacodynamics

Ceritinib displayed weak agonist activity in the *in vitro* functional assay of the Dopamine D2 receptor (EC_{50} of 6.0 µM). Ceritinib inhibited insulin receptor (INSR) with approximately 50 times less potency than ALK in a biochemical assay (INSR IC_{50} = 7 nM vs. ALK IC_{50} = 0.15 nM). When evaluated in the oral glucose tolerance test in mice under the fasting condition, ceritinib was found to have no significant effect on glucose metabolism up to 100 mg/kg/day, a dose level that is 4-time higher than the dose that led to the regression of ALK-dependent tumors.

Safety Pharmacology

Safety pharmacology studies indicate that ceritinib is unlikely to interfere with vital functions of the respiratory and central nervous systems. *In vitro* data show that the IC_{50} for the inhibitory effect of ceritinib on the hERG potassium channel was 0.4 micromolar at 33°C to 35°C (near body temperature). An *in vivo* telemetry study in monkeys showed a modest QT prolongation in 1 of 4 animals after receiving the highest dose of ceritinib. ECG studies in monkeys after 4- or 13-weeks of dosing with ceritinib have not shown QT prolongation or abnormal ECGs.

General Toxicology: Target organs in nonclinical animal models included, but were not limited to, the pancreas, biliopancreatic/bile ducts, gastrointestinal tract, liver, lung, lymphatic system and hematopoietic system.

Pancreatic focal acinar cell atrophy was observed in rats at 1.5-fold the human exposure by AUC at the recommended dose (RD). Biliopancreatic duct and bile duct necrosis/hyperplasia of epithelium were observed in rats and monkeys at exposures equal to or greater than the human exposure by AUC at the RD. 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 RD.

Gastrointestinal toxicity was observed in both species characterized by body weight loss, decreased food consumption, emesis (monkey), diarrhea, and at high doses, by histopathologic lesions including erosion, mucosal inflammation, and foamy macrophages in the duodenal crypts and submucosa at 1.4-fold the human exposure by AUC at the RD. Minimal necrosis and hemorrhage of the duodenum was exhibited in monkeys and rats at an exposure similar to that observed clinically.

Liver was also affected in both species, but only at the highest dose levels studied, and included minimal increases in liver transaminases in a few animals, and vacuolation of the intra-hepatic bile duct epithelium at exposures 1.4-fold the human exposure by AUC at the RD.

Alveolar foamy macrophages (confirmed phospholipidosis) were seen in the lungs of rats, but not in monkeys. Evidence of phospholipidosis (lung) occurred at exposures 1.4-fold the human exposure by AUC at the RD and was completely reversible. The human relevance of phospholipidosis is not known.

The mesenteric lymph nodes of rats and monkeys showed increased numbers of macrophages at exposures equivalent to human exposure by AUC at the RD, which was reversible. Thymus lymphoid depletion was observed in monkeys at exposures that were 1.4 fold the human exposures by AUC at the RD, and was reversible.
Effects were observed in the hematopoietic system, in both rats and monkeys, including increased monocytes, neutrophils, lymphocytes, and platelets and decreased reticulocytes and mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), hematocrit, and hemoglobin in rats and in monkeys, mild decreases in neutrophils, moderate decreases in reticulocytes and decreased cellularity in bone marrow were seen at exposures 1.4-fold of the human exposure by AUC at the RD, and were completely reversible. In the 13 week studies (at exposures equivalent to human exposure by AUC at the RD) hematological effects were seen only in rats (increased fibrinogen and platelets), and were reflective of inflammatory changes seen histologically in the biliopancreatic/hepatic ducts. The hematopoietic system was affected in rats (increased neutrophils) at exposures 1.4 fold of the human AUC exposure by AUC at the RD.
In 13-week study in monkeys, glucose concentrations were mildly increased, and reversible at exposures similar to human exposures by AUC at the RD. A mechanism for this modest effect was undetermined, but because animals were not fasted before sample collections, differences in relative timing of food consumption between arms and/or individuals may have impacted results.
Ceritinib crossed the blood brain barrier in rats with a brain-to-blood exposure (AUC_{inf}) ratio of approximately 15%.

Carcinogenicity: Carcinogenicity studies have not been performed with ceritinib.

Genotoxicity: Ceritinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay. Ceritinib was not clastogenic in the in vivo rat micronucleus assay (at exposures 40-fold the human exposure by AUC at the recommended dose). However, ceritinib induced numerical aberrations (aneugenic) in the in vitro cytogenetic assay using human lymphocytes (at a concentration 120-fold higher than the human recommended dose C_{max}), and micronuclei in the in vitro micronucleus test using TK6 cells. As such, ceritinib is considered genotoxic.

Phototoxicity: Ceritinib showed phototoxic potential in the 3T3 NRU in vitro assay (PIF=8.1), while a subsequent in vivo assessment of phototoxicity, the mouse ultraviolet local lymph node assay (UV LLNA), demonstrated that ceritinib is not phototoxic.

Reproductive and Developmental Toxicology: 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 (approximately 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 (approximately 0.72-fold the human exposure by AUC at the recommended dose). In addition, embryolethality was observed in rabbits at a dose of 50 mg/kg (approximately equivalent to the human exposure by AUC at the recommended dose). Formal non-clinical studies on the potential effects of ceritinib on fertility have not been conducted.

17 SUPPORTING PRODUCT MONOGRAPHS

N/A

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] ZYKADIA®

Ceritinib Capsules

Read this carefully before you start taking **ZYKADIA®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ZYKADIA.**

Serious Warnings and Precautions

ZYKADIA should be prescribed and used only under the supervision of a healthcare professional experienced with drugs used to treat cancer.
Serious side effects with ZYKADIA include:

- Heart problems (QT interval prolongation).
- Lung disorders, such as interstitial lung disease or pneumonitis. These may result in death.
- Liver problems.
- Gastrointestinal Reactions: Stomach and intestinal problems.

ZYKADIA has not been studied in patients with severe kidney problems who require dialysis.

What is ZYKADIA used for?

ZYKADIA is used to treat adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (a cancer that cannot be surgically removed for cure) or metastatic (a cancer that has spread to other parts of the body) non-small cell lung cancer (NSCLC) who have progressed on (their cancer got worse) or who were intolerant to (unable to take) the drug crizotinib. Refer to the NOC/c summary box below for additional detail.

ZYKADIA is also used to treat adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (a cancer that cannot be surgically removed for cure) or metastatic (a cancer that has spread to other parts of the body) non-small cell lung cancer (NSCLC).

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

For the following indication ZYKADIA has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced (a cancer that cannot be surgically removed for cure) or metastatic (a cancer that has spread to other parts of the body) non-small cell lung cancer (NSCLC) who have progressed on (their cancer got worse) or who were intolerant to (unable to take) the drug crizotinib.

For the following indication ZYKADIA has been approved without conditions. This means it has passed Health Canada's review and can be bought and sold in Canada.

- for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive

locally advanced (a cancer that cannot be surgically removed for cure) or metastatic (a cancer that has spread to other parts of the body) non-small cell lung cancer (NSCLC).

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does ZYKADIA work?

ZYKADIA belongs to a group of anti-tumor medicines which stop cancer from making new cells if the cancer is caused by a defect in a gene called anaplastic lymphoma kinase (ALK). ZYKADIA may slow down the growth and spread of non-small cell lung cancer (NSCLC).

What are the ingredients in ZYKADIA?

Medicinal ingredients: Ceritinib

Non-medicinal ingredients: black iron oxide; colloidal anhydrous silica; gelatin; indigotine; hydroxypropylcellulose, low-substituted; magnesium stearate; microcrystalline cellulose; sodium starch glycolate; titanium dioxide

ZYKADIA comes in the following dosage forms:

Capsules; 150 mg

Do not use ZYKADIA if:

- are allergic to ceritinib, or any non-medicinal ingredients in the formulation.
- have congenital long QT syndrome – a heart disorder that you were born with.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ZYKADIA. Talk about any health conditions or problems you may have, including if you:

- have/had problems with your liver.
- have/had diabetes or high blood sugar.
- have/had problems with your lungs or problems breathing.
- have/had problems with your heart, including a condition called long QT syndrome.
- have/had problems with your pancreas.
- have a history of fainting.
- have a family history of sudden cardiac death at less than 50 years of age.

- have electrolyte disturbances such as hypokalemia (low potassium in the blood), hypomagnesemia (low magnesium in the blood) or hypocalcemia (low calcium in the blood) or suffer from excessive vomiting or an eating disorder.
- are currently taking steroid medications.
- are pregnant, think you may be pregnant, or plan to become pregnant.
- are breast-feeding or plan to breast-feed.

Other warnings you should know about:

Women who might get pregnant (women of child-bearing age) and Males

Both men and women must use a highly effective method of birth control during treatment with ZYKADIA and for 3 months after stopping ZYKADIA. Talk to your healthcare professional about the birth control methods that may be right for you.

Pregnancy and breast-feeding

- **Pregnant women**

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

- **Breast-feeding mothers**

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

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ZYKADIA:

- Medicines used to treat irregular heart beat such as anti-arrhythmics: quinidine, amiodarone, disopyramide, procainamide, sotalol, ibutilide, dronedarone, flecainide, propafenone;
- Medicines used to stabilize thinking and behaviour, such as chlorpromazine, droperidol, haloperidol, ziprasidone;
- Medicines used to treat mood disorder such as fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants (e.g. amitriptyline, imipramine, maprotiline, nefazodone) or medicines used to treat psychosis such as pimozide;
- Medicines used to prevent and treat pneumocystis carinii pneumonia such as pentamidine;
- Medicines used to treat malaria such as quinine, chloroquine;
- Medicines used to treat AIDS/HIV such as ritonavir or saquinavir;
- Medicines used to treat infections. These include medicines which treat fungal infections, such as antifungals like ketoconazole, itraconazole, fluconazole, voriconazole or posaconazole, or medicines which treat certain types of bacterial infections, such as antibiotics like azithromycin, moxifloxacin, levofloxacin, ciprofloxacin, erythromycin, clarithromycin, telithromycin, tacrolimus;
- Medicines that decrease electrolyte levels (water pills, laxatives);
- Pentamidine;
- Methadone;

- Medicines for nausea and vomiting such as ondansetron or medicines that may increase the motility in the upper gastrointestinal tract such as domperidone;
- Other cancer medicines such as vorinostat, sunitinib, nilotinib, lapatinib, and vandetanib;
- Medicines used to treat asthma such as formoterol and salmeterol;
- Arsenic trioxide- a natural product used to treat certain types of cancers;
- St. John's Wort - an herbal product used to treat depression and other conditions, also known as Hypericum perforatum;
- Medicines which stop seizures or fits (anti-epileptics such as phenytoin, carbamazepine, or phenobarbital);
- Medicines used to treat tuberculosis such as rifampin or rifabutin;
- Midazolam, a medicine used to treat acute seizures, or as a sedative before or during surgery or medical procedures;
- Warfarin, an anticoagulant medicine used to prevent blood clots;
- Diclofenac, a medicine used to treat joint pain and inflammation;
- Cyclosporine, tacrolimus and sirolimus, medicines used in organ transplantation to prevent transplant organ rejection;
- Dihydroergotamine and ergotamine, medicines used to treat migraine;
- Medicines used to treat heartburn and indigestion such as antacids and H2 blockers;
- Alfentanil and fentanyl, medicines used to treat severe pain.

Ask your healthcare professional if you are not sure whether your medicine is one of the medicines listed above.

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

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

You should also tell your healthcare professional if you are already taking ZYKADIA and you are prescribed a new medicine that you have not taken previously during treatment with ZYKADIA.

How to take ZYKADIA:

- Exactly as your healthcare professional has told you.
- Once a day at the same time each day.
- Take with food (for example a snack or full meal).
- Swallow whole with water. Do NOT chew or crush capsules.
- If vomiting occurs after you swallow ZYKADIA capsules, do not take any more until your next scheduled dose.

<u>How long to take ZYKADIA</u>

- Continue for as long as your healthcare professional tells you.
- This is a long-term treatment that might last for months. Your healthcare professional will monitor your condition to be sure that the treatment is having the desired effect.

If you have questions about how long to take ZYKADIA, talk to your healthcare professional.

Usual dose:

Maximum Recommended Dose: 450 mg once a day with food.

Do not change the dose without talking to your healthcare professional.

If you have certain side effects your healthcare professional may interrupt, decrease or stop ZYKADIA.

Dosing for Patients with Gastrointestinal Reactions: If you have diarrhea, nausea or vomiting your healthcare professional may lower your dose. This may help to decrease these problems.

Overdose:

If you think you, or a person you are caring for, have taken too much ZYKADIA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed 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 are possible side effects from using ZYKADIA?

These are not all the possible side effects you may have when taking ZYKADIA. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Diarrhea
- Nausea
- Vomiting
- Abdominal pain
- Tiredness, fatigue
- Decreased appetite
- Weight loss
- Constipation
- Heartburn, indigestion
- Difficulty swallowing
- Pain in the back or extremities (hands, arms, feet and legs)
- Rash
- Numbness and tingling in the hands and/or feet
- Vision problems

ZYKADIA can cause abnormal test results. You can especially get high blood sugar, bilirubin or liver enzymes. These can include alanine aminotransferase (ALT), aspartate aminotransferase (AST) gamma glutamyltransferase (GGT), or blood alkaline phosphatase.

Your healthcare professional should do tests, before you start and regularly during your treatment. They can monitor your blood pressure, heart rate by ECG. Blood tests can be used to check on your health and on the blood, liver and kidneys. Your healthcare professional will decide when to perform tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Liver Disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite, itching skin			√
Anemia: fatigue, loss of energy, weakness, shortness of breath		√	
COMMON			
Heart disorders (Bradycardia, QT prolongation): ECG changes, irregular or slow heartbeat, heart palpitations, dizziness, fainting or loss of consciousness			√
Lung disorders (pneumonia, pneumonitis), respiratory failure: Cough, difficult or painful breathing, wheezing, pain in chest when breathing, fever. Increased breathing rate, sudden worsening of shortness of breath, bluish colour on skin, lips and fingernails. Irregular heartbeats, feel sleepy, loss of consciousness			√
Kidney Disorder: change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		√	
Increased blood sugar (hyperglycemia): frequent urination, thirst, and hunger		√	
Decreased levels of phosphate in the blood: muscle pain and weakness, altered mental state		√	
Convulsion: seizure, spasms, shaking or fits			√
Pericardial Effusion, pericarditis (fluid around the heart, inflammation of the lining surrounding the heart): Chest pain or pressure, shortness of breath, nausea, abdominal fullness,			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
difficulty swallowing, sharp, stabbing chest pain that gets worse when you cough, swallow, breathe deeply or lie flat			
Chest pain or discomfort		√	
Severe nausea, vomiting and/or diarrhea, dehydration: Thirst, headache, general discomfort, loss of appetite, decreased urine, confusion, unexplained tiredness		√	
Headache		√	
General Physical Health Deterioration		√	
UNCOMMON:			
Gastrointestinal Bleeding in the stomach or bowels: Black, tarry stool, blood in the stool		√	
Inflammation of the pancreas (Pancreatitis): abdominal pain that lasts and gets worse when you lie down; nausea, vomiting			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Do not take ZYKADIA after the expiry date stated on the box.

Store in the original package. Do not store above 30°C.

Do not take this medicine if you notice any damage to the packaging or if there are any signs of tampering. Ask your pharmacist how to throw away medicines you no longer use.

Keep out of reach and sight of children.

If you want more information about ZYKADIA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.novartis.ca or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

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ZYKADIA is a registered trademark.

Novartis Version

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