PRODUCT INFORMATION

ZYKADIA®

Ceritinib

SERIOUS ADVERSE EVENTS

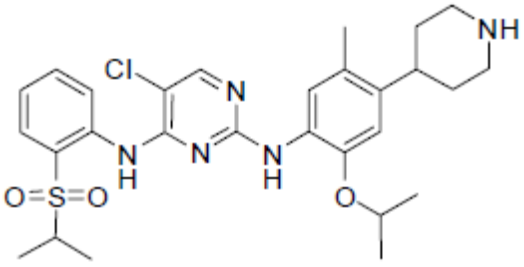
The following severe adverse events have been seen. Monitor closely and consider early dose reduction. See referenced () sections for details and appropriate management.

•QT interval prolongation (see Pharmacokinetics, Precautions, Adverse Effects, Dosage & Administration)
•Interstitial Lung Disease/Pneumonitis, including fatal cases (see Precautions, Adverse Effects, Dosage & Administration).
•Hepatotoxicity, including drug-induced liver injury (Pharmacokinetics, Precautions, Adverse Effects, Dosage & Administration).
•Gastrointestinal toxicity (Precautions, Adverse Effects, Dosage & Administration).

ZYKADIA has not been studied in patients with moderate and severe hepatic impairment.

ZYKADIA must be taken while fasting – any food consumption within a 2 hour period before or after administration, increases systemic exposure up to 2-fold increasing the risk of toxicities, and also potentially exceeds the maximum dose tested, and the risks are unknown (see Pharmacokinetics, Dosage and Administration).

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



INN: ceritinib (free base)

CAS: 1032900-25-6

DESCRIPTION

The active ingredient in Zykadia 150 mg hard capsules is ceritinib. Ceritinib is white to almost white or light yellow or light brown powder that has good solubility in very acidic aqueous medium. The solubility decreases significantly with increasing pH. The pH of a 1% aqueous suspension of ceritinib in water is 6.86 and melting point 174.0°C.

Each Zykadia capsule contains 150 mg of active ingredient (ceritinib). The capsule inactive contents are microcrystalline cellulose, hyprolose, sodium starch glycolate type A, magnesium stearate, colloidal anhydrous silica.

The hard gelatin capsule shell contains gelatin, titanium dioxide, indigo carmine. The printing ink is OPACODE monogramming ink S-1-277002 BLACK.

PHARMACOLOGY

PHARMACODYNAMICS

Mechanisms of action

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

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

PHARMACOKINETICS

Absorption

Peak plasma levels (C_{max}) of ceritinib are achieved approximately 4 to 6 hours after oral administration in patients. Oral absorption was estimated to be ≥25% based on metabolite percentages in the faeces. The maximum possible absolute oral bioavailability of ceritinib from the capsules is estimated at approximately ≤58%.

Systemic exposure to ceritinib is increased when administered with food. A food effect study conducted in healthy subjects with a single 500 mg ceritinib dose showed that a high-fat meal increased ceritinib AUC by 73% and C_{max} by 41% and a low-fat meal increased ceritinib AUC by 58% and C_{max} by 43% as compared with the fasted state. Ceritinib should be taken on an empty stomach. No food should be eaten for at least two hours before and two hours after the

dose of ZYKADIA is taken (see Boxed Warning, Interactions with other Medicines, Dosage and Administration).

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

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

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

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

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

Elimination
Following single oral doses of ceritinib, the geometric mean apparent plasma terminal half-life ($T_{1/2}$) of ceritinib ranged from 31 to 41 hours in patients over the 400 to 750 mg dose range. Daily oral dosing of ceritinib results in achievement of steady-state by approximately 15 days and remains stable afterwards, with a geometric mean accumulation ratio of 6.2 after 3 weeks of daily dosing. The geometric mean apparent clearance (CL/F) of ceritinib was lower at steady-state (33.2 L/hr) after 750 mg daily oral dosing than after a single 750 mg oral dose (88.5 L/hr) suggesting that ceritinib demonstrates non-linear PK over time.

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

Special populations

Patients with hepatic impairment

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

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

Patients with renal impairment

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

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

Effects of age, gender, and race

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

Cardiac electrophysiology

Ceritinib inhibited hERG channel activity in an *in vitro* assay (IC_{50} 0.4μM). The potential for QT interval prolongation of ceritinib was assessed in 4 clinical studies with ZYKADIA. Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of ceritinib on the QT interval. A central analysis of ECG data demonstrated new QTc >500 msec in 1 patient (0.2%). There were 23 patients (4.4%) with a QTc increase from baseline >60 msec. A concentration-QTc response analysis based on the data from a global phase 1 study (Study A) demonstrated that at average steady-state concentrations the upper bound of the 2-sided 90% CI for QTc was 16 msec at ZYKADIA 750 mg. A pharmacokinetic analysis suggested that ceritinib

causes concentration-dependent increases in QTc (see Boxed Warning, Precautions, Adverse Effects, Dosage and Administration).

CLINICAL TRIALS

ZYKADIA is approved as monotherapy on the basis of overall response rate and duration of response rate from two single arm open label phase I and II studies. Patients should be advised of the fact that the approval required submission to the TGA of a phase III study (already underway) designed to provide further efficacy and safety data.

The use of Zykadia in the treatment of ALK-positive NSCLC patients previously treated with an ALK inhibitor was investigated in two global, multicentre, open-label, single-arm studies (Study X2101 and Study A2201).The primary efficacy endpoint for these studies was overall response rate (ORR) for patients who were treated with a ZYKADIA dose of 750 mg, defined as the proportion of patients with best response of complete response (CR) or partial response (PR) confirmed by repeat assessments performed not less than 4 weeks after the criteria for response was first met. Additional evaluations included duration of response (DOR) and progression-free survival (PFS) by Investigator assessment, and overall survival (OS). Tumour evaluations were performed by the investigator according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.0 in Study X2101 and RECIST 1.1 in Study A2201.

Study X2101 was a global, multicenter, open-label, phase 1 study which included a dose-escalation phase and an expansion phase, at the recommended dose of 750 mg. All patients enrolled in the study had locally advanced or metastatic malignancy that had progressed despite standard therapy and all patients were previously tested for ALK rearrangement. Patients with controlled or asymptomatic brain metastases were eligible for the study. A total of 246 ALK-positive NSCLC patients were enrolled who were treated at a ZYKADIA dose of 750 mg, 163 had received prior treatment with an ALK inhibitor.

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

Study A2201 was a global, multicenter, open-label, single-arm, phase 2 study designed to evaluate the efficacy and safety of 750 mg ceritinib in patients with locally advanced or metastatic ALK-positive NSCLC. Study A2201 enrolled 140 patients who had been previously treated with 1 to 3 prior lines of cytotoxic chemotherapy followed by treatment with crizotinib, and who had then progressed on crizotinib.

In Study A2201, the median age was 51 years (range: 29 to 80 years); 87.1% of patients were younger than 65 years. A total of 50.0% of patients were female. Caucasians comprised 60.0% of the study population, Asians 37.9% and other races 2.1%. The vast majority of patients had adenocarcinoma (92.1%). All patients were treated with 2 or more regimens prior to enrolment into the study.

Main efficacy results from Studies X2101 and A2201

The main efficacy data for studies X2101 and A2201 are summarized in Table 1. Final overall survival data are presented for Study A2201. For study X2101 OS data were not yet mature at the time of the analysis.

Table 1 Overview of efficacy data in ALK-positive NSCLC patients from studies X2101 and A2201

	Study X2101 ceritinib 750 mg N=163	**Study A2201 ceritinib 750 mg N=140**
Duration of follow-up		
Median (months) (min – max)	10.2 (0.1 – 24.1)	14.1 (0.1 – 35.5)
Overall response rate investigator (CR + PR), n (%)	92 (56.4)	57 (40.7)
(95% CI)	(48.5, 64.2)	(32.5, 49.3)
Overall response rate BIRC (CR + PR), n (%)	75 (46.0)	50 (35.7)
(95% CI)	(38.2, 54.0)	(27.8, 44.2)
Duration of response* investigator		
Median (months) (95% CI)	8.3 (6.8, 9.7)	10.6 (7.4, 14.7)
Duration of response* BIRC		
Median (months) (95% CI)	8.8 (6.0, 13.1)	12.9 (9.3, 18.4)
Progression-free survival investigator		
Median (months) (95% CI)	6.9 (5.6, 8.7)	5.8 (5.4, 7.6)
Progression-free survival BIRC		
Median (months) (95% CI)	7.0 (5.7, 8.6)	7.4 (5.6, 10.9)

Overall survival		
Median (months) (95% CI)	16.7 (14.8, NE)	15.6 (13.6, 24.2)

NE = not estimable
Study X2101: Responses assessed by Investigator using RECIST 1.0
Study A2201: Responses assessed by Investigator using RECIST 1.1
CR, PR confirmed by repeat assessments performed not less than 4 weeks after response criteria were first met
**Includes only patients with confirmed CR, PR*

Patients with brain metastases

In Studies X2101 and A2201, brain metastases were seen in 60.1% and 71.4% of patients who had received prior ALK inhibitor treatment, respectively. The ORR, DOR (for patients with confirmed PR or CR) and PFS (by blinded independent review committee assessment (BIRC)) for patients with brain metastases at baseline were in line with those reported with the overall population of these studies.

INDICATIONS

ZYKADIA is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on or who are intolerant of crizotinib.

Note to Indication: This indication is approved based on tumour response rates and duration of response. An improvement in survival or disease –related symptoms has not been established.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS

HEPATOTOXICITY

Cases of hepatotoxicity occurred in less than 1% of patients treated with ZYKADIA in clinical studies. Cases of abnormal liver function tests occurred in 2.1% of patients treated with ZYKADIA in clinical studies. Cases of drug induced liver injury have been observed in 2 out of 525 (0.4%) of patients treated with ZYKADIA in clinical studies. Increases to grade 3 or 4 ALT elevations were observed in 25% of patients receiving ZYKADIA. Concurrent elevations in ALT greater than three times the upper limit of normal and total bilirubin greater than two times the upper limit of normal, with normal alkaline phosphatase, occurred in less than 1% of patients in clinical studies. Hepatotoxicity events were managed with dose interruptions or reductions in

34.3% of patients. Less than 1% of patients required permanent discontinuation of treatment in clinical studies with ceritinib. Few events required discontinuation of ZYKADIA.

Monitor with liver laboratory tests (including ALT, AST, and total bilirubin) prior to the start of treatment and monthly thereafter. Patients should be monitored for liver laboratory test abnormalities and managed as recommended in Dosage and Administration. In patients who develop transaminase elevations, more frequent monitoring of liver transaminases and total bilirubin should be done as clinically indicated (see Dosage and Administration and Adverse Events). Ceritinib is not recommended for patients with moderate to severe hepatic impairment.

INTERSTITIAL LUNG DISEASE/PNEUMONITIS

Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis have been observed in patients treated with ZYKADIA in clinical studies. In clinical studies, any grade ILD/pneumonitis has been reported in 3.2% of patients treated with ceritinib, and grade 3 or 4 events have been reported in 1.9% of patients. Monitor patients for pulmonary symptoms indicative of pneumonitis. Exclude other potential causes of pneumonitis, and discontinue ZYKADIA in patients diagnosed with treatment-related pneumonitis, any grade (see Dosage and Administration and Adverse Events).

QT INTERVAL PROLONGATION

QTc prolongation has been observed in clinical studies in patients treated with ZYKADIA, which may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade de pointes) or sudden death. In clinical studies, 6.5% of patients treated with ceritinib had events of QT prolongation (any grade), including grade 3 or 4 events in 0.8% of patients. These events required dose reduction or interruption in 1% of patients and led to discontinuation in 0.2% of patients.

A central analysis of ECG data demonstrated new QTc >500 msec in 1 patient (0.2%). There were 23 patients (4.4%) with a QTc increase from baseline >60 msec. A pharmacokinetic analysis suggested that ceritinib causes concentration-dependent increases in QTc.

Treatment with ceritinib is not recommended in patients who have congenital long QT syndrome or who are taking medicinal products known to prolong the QTc interval. Periodic monitoring with ECGs and periodic monitoring of electrolytes (e.g., potassium) is recommended in patients with congestive heart failure, bradyarrhythmias, or electrolyte abnormalities and in patients who are taking medications that are known to prolong the QT interval. Particular care should be exercised when administering ceritinib to patients with an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging medicinal product. In case of vomiting, diarrhoea, dehydration, or impaired renal function, correct electrolytes as clinically indicated. Permanently discontinue ZYKADIA in patients who develop QTc greater than 500 msec or greater than 60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. Withhold ZYKADIA in patients who

develop QTc greater than 500 msec on at least 2 separate ECGs until recovery to baseline or a QTc less than 481 msec, then reinitiate ZYKADIA by reducing dose by one decrement (see Dosage and Administration, Adverse Events and Pharmacokinetics; Special Population).

BRADYCARDIA

In clinical studies, bradycardia and/or sinus bradycardia (heart rate less than 60 bpm) events (all grade 1) were reported in 1.9% of patients. None of these events led to dose reduction or interruption or to discontinuation of ceritinib treatment. Asymptomatic cases of bradycardia (heart rate less than 60 bpm) have been observed in 10 out of 525 (1.9%) patients treated with ZYKADIA in clinical studies. Use of ZYKADIA in combination with other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) should be avoided as far as possible. Monitor heart rate and blood pressure regularly. In cases of symptomatic bradycardia that is not life-threatening, withhold ZYKADIA until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, evaluate the use of concomitant medications, and adjust the dose of ZYKADIA if necessary. Permanently discontinue ZYKADIA for life-threatening bradycardia if no contributing concomitant medication is identified; however, if associated with concomitant medication known to cause bradycardia or hypotension, withhold ZYKADIA until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If concomitant medication can be adjusted or discontinued, reinitiate ZYKADIA by reducing dose by two decrements upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring (see Dosage and Administration and Adverse Events).

GASTROINTESTINAL TOXICITY

Across four clinical studies, gastrointestinal toxicity (all grades) occurred in 97.9% of patients treated at a dose of 750 mg. Diarrhoea, nausea and vomiting occurred in 83.8%, 79.8% and 62.9% of patients, respectively. Persistent grade 1-2 nausea, vomiting and diarrhoea requiring dose reduction have been observed. Grade 3-4 (severe) diarrhoea, nausea and vomiting occurred in 5.3%, 5.3% and 4.6% of patients, respectively. Nausea led to dose discontinuation in 2 patients (0.4%), and nausea and vomiting led to dose discontinuation in 1 patient (0.2%). Nausea, vomiting, and diarrhoea led to dose adjustments or interruptions in 18.7%, 18.7%, and 16.0%, respectively.

Gastrointestinal events were managed primarily with concomitant medicinal products including anti-emetic/anti-diarrhoeal medicinal products (in 84.8% of patients) and/or with dose reduction or interruption (in 33.0% of patients). Gastrointestinal events led to discontinuation in 0.6% of patients.

Monitor and manage patients using standards of care, including anti-diarrhoeals, anti-emetics, or fluid replacement, as indicated. Dose interruption and dose reduction may be employed as necessary (see Dosage and Administration and Adverse Events). If vomiting occurs during the

course of treatment, the patient should not take an additional dose, but should continue with the next scheduled dose.

HYPERGLYCAEMIA

Events of hyperglycaemia (all grades) have been reported in 7.8% of patients treated with ZYKADIA in clinical studies; 5% of patients reported a grade 3/4 event. These events required dose reduction or interruption in 1.3% of patients and led to discontinuation in 0.2% of patients. The risk of hyperglycaemia was higher in patients with diabetes mellitus and/or concurrent steroid use. Events of diabetes mellitus (all grades) have been reported in 3.2% of patients treated with ZYKADIA in clinical studies.

Monitor fasting serum glucose prior to the start of ZYKADIA treatment and periodically thereafter as clinically indicated. Initiate or optimize anti-hyperglycaemic medications as indicated (see Dosage and Administration and Adverse Events).

PANCREATIC TOXICITY

Across the four clinical studies, AEs of amylase increased (all grades) occurred in 4.6% of patients receiving ZYKADIA; 1.9% of patients reported a grade 3-4 event. In Study X2101, AEs of lipase increased (all grades) occurred in 4.6% of patients receiving ZYKADIA; 3.0% of patients reported a grade 3-4 event.

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 Dosage and Administration and Adverse Effects).

EFFECTS ON FERTILITY

The potential for ZYKADIA to cause infertility in male and female patients is unknown. The potential effects on fertility have not been assessed in animal studies. 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. The effectiveness of concomitant administration of oral contraceptives may be reduced (see Interactions with Other Medicines)

USE IN PREGNANCY – Category D

There are no data regarding the use of ZYKADIA in pregnant women. Based on its mechanism of action, Zykadia may cause fetal harm when administered to a pregnant woman. ZYKADIA should not be given to a pregnant women unless the potential benefits for her outweigh the potential risk to the fetus.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.

Women of childbearing potential should be advised to use a highly effective method of contraception noting the potential for ceritinib to decrease the effectiveness of the oral contraceptive (see Interactions with Other Medicines) while receiving ZYKADIA and for up to 3 months after discontinuing treatment.

In an embryofetal 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 (0.6-fold the human exposure by AUC at the recommended dose). Findings included delayed ossifications and skeletal variations (wavy ribs).

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 0.02-fold the human exposure by AUC at the recommended dose). A low incidence of visceral anomalies, including absent or malpositioned gallbladder and retro-oesophageal subclavian cardiac artery, was observed at doses equal to or greater than 10 mg/kg/day (approximately 0.1-fold the human exposure by AUC at the recommended dose). Maternal toxicity and abortion occurred in rabbits at doses of 35 mg/kg or greater. In addition, embryolethality was observed in rabbits at a dose of 50 mg/kg.

USE IN LACTATION

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

PAEDIATRIC USE

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

USE IN ELDERLY

Across four clinical studies, 89 of 525 patients (17.0%) treated with ZYKADIA were aged 65 years and older. The safety profile in patients aged 65 years and older was similar to that in patients less than 65 years of age (see Dosage and Administration and Pharmacokinetics; Special Population). There are no available data on patients over 85 years of age.

GENOTOXICITY

Ceritinib induced polyploidy in human lymphocytes and a small increase in micronuclei in TK6 cells *in vitro*. However, it was not mutagenic *in vitro* in the bacterial gene mutation assay and not clastogenic in human lymphocytes *in vitro* and in a rat micronucleus assay *in vivo*. Ceritinib has a low risk of genotoxicity in patients.

CARCINOGENICITY

Carcinogenicity studies have not been performed with ceritinib.

INTERACTIONS WITH OTHER MEDICINES

Agents that may increase ceritinib plasma concentrations

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

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

Agents that may decrease ceritinib plasma concentrations

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

Gastric acid-reducing agents (e.g. proton pump inhibitors [PPIs], H2-receptor antagonists, antacids) may reduce the bioavailability of ceritinib as it demonstrates reduced solubility with increased pH in vitro. In healthy subjects (N=22), administration of esomeprazole (a PPI) at 40 mg daily for six days resulted in decreased exposure to a single dose of 750 mg of ceritinib co-administered on the sixth day (ceritinib AUCinf and Cmax were decreased by 76% and 79%, respectively). A dedicated study to evaluate the effect of gastric acid-reducing agents on ceritinib exposure in patients under recommended dosing and steady-state conditions has not been conducted, and data for H2 receptor antagonists and antacids is lacking. Caution is advised with concomitant use of gastric acid-reducing agents, particularly PPIs.

Agents whose plasma concentration may be altered by ceritinib

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

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

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

Agents that are substrates of transporters

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

Drug-food/drink interactions

The bioavailability of ceritinib is increased in the presence of food depending on the fat content in the meal (see Pharmacokinetics; Absorption). Ceritinib should be taken on an empty stomach. No food should be eaten for at least two hours before and two hours after the dose of ZYKADIA is taken in order to avoid systemic exposure exceeding that of a 750 mg ZYKADIA dose taken in the fasted state, which may increase adverse drug reactions (see Pharmacokinetics, Absorption; Dosage and Administration). 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.

ADVERSE EFFECTS

There are limitations in identifying safety issues in small single arm, open-label studies. Clinical trials are conducted under very specific conditions hence the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Summary of the safety profile

The data described below reflect exposure to ZYKADIA in 525 patients with tumours confirmed to have a genetic abnormality in ALK (515 ALK-positive NSCLC patients and 10 ALK-positive non-NSCLC patients) and treated at the 750 mg dose in four clinical studies.

The median duration of exposure to ZYKADIA was 33.0 weeks (range 0.3 to 106.1 weeks). Dose reductions occurred in 57.7% of patients and dose interruptions in 73.5% of patients.

The rate of adverse events (AEs) resulting in permanent discontinuation was 8.8%. The most frequent AEs leading to discontinuation were pneumonia (0.8%), pneumonitis (0.8%), and nausea (0.6%).

In the pooled dataset (Table 2) the most frequent AEs (>25% of patients, irrespective of relationship to study drug) in the pooled dataset were those associated with GI toxicity events (diarrhoea 83.8%, nausea 79.8%, vomiting 62.9%) and increased transaminases (ALT increased 41.7%, AST increased 31.2%). Grade 3-4 AEs were seen in 73.1% of all patients. The most frequent (≥ 5% of patients) grade 3-4 AEs were ALT increased (21.9%), GGT increased (9.0%), AST increased (7.8%), fatigue (5.5%), diarrhoea (5.3%), nausea (5.3%), and hyperglycaemia (5.0%).

Table 2 Frequent adverse events (pooled dataset, >5% of patients for all grades, or >2% of patients for grade 3-4)

	Study X2101		**Study A2203***		**Study A2201**		**Study X1101***		**All patients**	
	Ceritinib 750 mg		Ceritinib 750 mg		Ceritinib 750 mg		Ceritinib 750 mg		Ceritinib 750 mg	
	N=255		N=124		N=140		N=6		N=525	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Diarrhoea	221 (86.7)	15 (5.9)	102 (82.3)	4 (3.2)	112 (80.0)	9 (6.4)	5 (83.3)	0	440 (83.8)	28 (5.3)
Nausea	211 (82.7)	15 (5.9)	92 (74.2)	4 (3.2)	111 (79.3)	9 (6.4)	5 (83.3)	0	419 (79.8)	28 (5.3)
Vomiting	157 (61.6)	12 (4.7)	83 (66.9)	6 (4.8)	87 (62.1)	6 (4.3)	3 (50.0)	0	330 (62.9)	24 (4.6)
Alanine Aminotransferase Increased	112 (43.9)	76 (29.8)	50 (40.3)	19 (15.3)	56 (40.0)	19 (13.6)	1 (16.7)	1 (16.7)	219 (41.7)	115 (21.9)
Decreased Appetite	95 (37.3)	4 (1.6)	61 (49.2)	2 (1.6)	56 (40.0)	5 (3.6)	4 (66.7)		216 (41.1)	11 (2.1)
Fatigue	110 (43.1)	13 (5.1)	40 (32.3)	7 (5.6)	46 (32.9)	9 (6.4)	3 (50.0)	0	199 (37.9)	29 (5.5)
Abdominal Pain	98 (38.4)	3 (1.2)	41 (33.1)	0	43 (30.7)	2 (1.4)	2 (33.3)	0	184 (35.0)	5 (1.0)
Aspartate Aminotransferase Increased	83 (32.5)	25 (9.8)	38 (30.6)	9 (7.3)	42 (30.0)	7 (5.0)	1(16.7)	0	164 (31.2)	41 (7.8)
Constipation	79 (31.0)	0	19 (15.3)	0	33 (23.6)	3 (2.1)	1 (16.7)	0	132 (25.1)	3(0.6)
Weight increased	46 (18.0)	5 (2.0)	36 (29.0)	1 (0.8)	45 (32.1)	6 (4.3)	0	0	127 (24.2)	12 (2.3)
Cough	74 (29.0)	0	21 (16.9)	0	26 (18.6)	0	0	0	121 (23.0)	0
Dyspnoea	63 (24.7)	11 (4.3)	17 (13.7)	1 (0.8)	25 (17.9)	7 (5.0)	0	0	105 (20.0)	19 (3.6)
Blood Creatinine Increased	43 (16.9)	0	26 (21.0)	0	20 (14.3)	0	4 (66.7)	0	93 (17.7)	0
Blood Alkaline Phosphatase Increased	45 (17.6)	13 (5.1)	25 (20.2)	8 (6.5)	21 (15.0)	4 (2.9)	1 (16.7)	0	92 (17.5)	25 (4.8)
Asthenia	50 (19.6)	2 (0.8)	18 (14.5)	2 (1.6)	22 (15.7)	6 (4.3)	0	0	90 (17.1)	10 (1.9)
Abdominal Pain Upper	60 (23.5)	2 (0.8)	11 (8.9)	0	16 (11.4)	1 (0.7)	1 (16.7)	0	88 (16.8)	3 (0.6)
Back pain	50 (19.6)	1 (0.4)	19 (15.3)	1 (0.8)	18 (12.9)	1 (0.7)	0	0	87 (16.6)	3 (0.6)
Pyrexia	42 (16.5)	0	13 (10.5)	1 (0.8)	29 (20.7)	4 (2.9)	2 (33.3)	0	86 (16.4)	5 (1.0)
Headache	51 (20.0)	4 (1.6)	11 (8.9)	1 (0.8)	20 (14.3)	0	0	0	82 (15.6)	5 (1.0)
Rash	34 (13.3)	0	19 (15.3)	1 (0.8)	20 (14.3)	0	1 (16.7)	0	74 (14.1)	1 (0.2)
Gamma-Glutamyltransfer-ase Increased	14 (5.5)	7 (2.7)	33 (26.6)	23 (18.5)	25 (17.9)	17 (12.1)	0	0	72 (13.7)	47 (9.0)

	Study X2101		Study A2203*		Study A2201		Study X1101*		All patients	
	Ceritinib 750 mg		Ceritinib 750 mg		Ceritinib 750 mg		Ceritinib 750 mg		Ceritinib 750 mg	
	N=255		N=124		N=140		N=6		N=525	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Non-Cardiac Chest Pain	26 (10.2)	2 (0.8)	16 (12.9)	1 (0.8)	23 (16.4)	2 (1.4)	0	0	65 (12.4)	5 (1.0)
Anaemia	31 (12.2)	13 (5.1)	8 (6.5)	1 (0.8)	20 (14.3)	3 (2.1)	1(16.7)	0	60 (11.4)	17 (3.2)
Insomnia	39 (15.3)	0	7 (5.6)	0	12 (8.6)	0	0	0	58 (11.0)	0
Musculoskeletal Pain	37 (14.5)	0	9 (7.3)	0	8 (5.7)	0	0	0	54 (10.3)	0
Dizziness	31 (12.2)	0	11 (8.9)	0	8 (5.7)	0	0	0	50 (9.5)	0
Dyspepsia	32 (12.5)	1 (0.4)	10 (8.1)	0	7 (5.0)	0	0	0	49 (9.3)	1 (0.2)
Hypokalaemia	29 (11.4)	11 (4.3)	11 (8.9)	5 (4.0)	8 (5.7)	4 (2.9)	0	0	48 (9.1)	20 (3.8)
Arthralgia	26 (10.2)	0	9 (7.3)	0	11 (7.9)	0	0	0	46 (8.8)	0
Oedema Peripheral	28 (11.0)	0	4 (3.2)	0	13 (9.3)	0	0	0	45 (8.6)	0
Upper respiratory tract infection	25 (9.8)	0	9(7.3)	0	11 (7.9)	0	0	0	45 (8.6)	0
Pneumonia	25 (9.8)	12 (4.7)	8 (6.5)	4 (3.2)	9 (6.4)	5 (3.6)	0	0	42 (8.0)	21 (4.0)
Hyperglycaemia	21 (8.2)	15 (5.9)	13 (10.5)	7 (5.6)	6 (4.3)	3 (2.1)	1 (16.7)	1 (16.7)	41 (7.8)	26 (5.0)
Musculoskeletal Chest Pain	27 (10.6)	0	3 (2.4)	0	7 (5.0)	0	0	0	37 (7.0)	0
Nasopharyngitis	19 (7.5)	0	10 (8.1)	0	6 (4.3)	0	0	0	35 (6.7)	0
Pruritus	17 (6.7)	1 (0.4)	12 (9.7)	0	6 (4.3)	0	0	0	35 (6.7)	1 (0.2)
Dry Skin	17 (6.7)	0	7 (5.6)	0	9 (6.4)	0	1 (16.7)	0	34 (6.5)	0
Electrocardiogram Qt Prolonged	10 (3.9)	3 (1.2)	15 (12.1)	1 (0.8)	9 (6.4)	0	0	0	34 (6.5)	4 (0.8)
Hypomagnesae-mia	23 (9.0)	0	3 (2.4)	1 (0.8)	7 (5.0)	0	1 (16.7)	0	34 (6.5)	1 (0.2)
Productive Cough	24 (9.4)	0	7 (5.6)	0	3 (2.1)	0	0	0	34 (6.5)	0
Dysgeusia	18 (7.1)	0	5 (4.0)	0	10 (7.1)	0	0	0	33 (6.3)	0
Anxiety	20 (7.8)	2 (0.8)	2 (1.6)	0	8 (5.7)	0	0	0	30 (5.7)	2 (0.4)
Stomatitis	13 (5.1)	0	7 (5.6)	1 (0.8)	10 (7.1)	0	0	0	30 (5.7)	1 (0.2)
Hypophosphatae-mia	16 (6.3)	8 (3.1)	5 (4.0)	1 (0.8)	6 (4.3)	2 (1.4)	1 (16.7)	0	28 (5.3)	11 (2.1)
Pain in extremity	19 (7.5)	0	2 (1.6)	0	7 (5.0)	0	0	0	28 (5.3)	0

	Study X2101		Study A2203*		Study A2201		Study X1101*		All patients	
	Ceritinib 750 mg		Ceritinib 750 mg		Ceritinib 750 mg		Ceritinib 750 mg		Ceritinib 750 mg	
	N=255		N=124		N=140		N=6		N=525	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Urinary tract infection	18 (7.1)	2 (0.8)	6 (4.8)	0	4 (2.9)	0	0	0	28 (5.3)	2 (0.4)
Lipase increased	24 (9.4)	16 (6.3)	0	0	0	0	0	0	24 (4.6)	16 (3.0)
Hyponatraemia	19 (7.5)	11 (4.3)	1 (0.7)	0	0	0	4 (3.2)	3 (2.4)	24 (4.6)	14 (2.7)

A patient with multiple severity ratings for an AE, is only counted under the maximum rating.
A patient with multiple AEs within a preferred term is counted only once in each preferred term.
Only AEs occurring during treatment or within 30 days of the last dose of study drug are reported.
AEs are graded according to the CTCAE V4.03; MedDRA version 17.0 is used.
**Study A2203: Phase II, multicenter, open-label, single-arm study to evaluate the efficacy and safety of 750 mg ceritinib in patients with locally advanced or metastatic ALK-positive NSCLC.*
**Study X1101: Phase I, open-label, dose-escalation and expansion study in Japanese Patients enrolling patients with ALK-positive solid tumors.*

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

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

Table 3 presents the frequency category of ADRs reported for ZYKADIA in patients treated at the starting dose of 750 mg in 4 clinical studies.

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

Table 3 Adverse drug reactions in 525 patients treated with ZYKADIA

Primary System Organ Class Preferred Term	All grades n (%)	Frequency category	Grades 3/4 n (%)	Frequency category
Blood and lymphatic system disorders				
Anemia	60 (11.4)	Very common	17 (3.2)	Common
Metabolism and nutrition disorders				
Decreased appetite	216 (41.1)	Very common	11 (2.1)	Common
Hyperglycemia	41 (7.8)	Common	26 (5.0)	Common
Hypophosphatemia	28 (5.3)	Common	11 (2.1)	Common
Eye disorders				
Vision disorder[m]	39 (7.4)	Common	0	
Cardiac disorders				
Pericarditis[h]	31 (5.9)	Common	16 (3.0)	Common
Bradycardia[e]	10 (1.9)	Common	0	
Respiratory, thoracic and mediastinal disorders				
Pneumonitis[i]	17 (3.2)	Common	10 (1.9)	Common
Gastrointestinal disorders				
Diarrhea	440 (83.8)	Very common	28 (5.3)	Common
Nausea	419 (79.8)	Very common	28 (5.3)	Common
Vomiting	330 (62.9)	Very common	24 (4.6)	Common
Abdominal pain[a]	253 (48.2)	Very common	8 (1.5)	Common
Constipation	132 (25.1)	Very common	3 (0.6)	Uncommon
Esophageal disorder[f]	79 (15.0)	Very common	2 (0.4)	Uncommon
Pancreatitis	2 (0.4)	Uncommon	2 (0.4)	Uncommon
Hepatobiliary disorders				
Abnormal liver function tests[c]	11 (2.1)	Common	8 (1.5)	Common

Primary System Organ Class Preferred Term	All grades n (%)	Frequency category	Grades 3/4 n (%)	Frequency category
Hepatotoxicity[d]	3 (0.6)	Uncommon	3 (0.6)	Uncommon
Skin and subcutaneous tissue disorders				
Rash[j]	100 (19.0)	Very common	2 (0.4)	Uncommon
Renal and urinary disorders				
Renal failure[k]	11 (2.1)	Common	1 (0.2)	Uncommon
Renal impairment[l]	7 (1.3)	Common	1 (0.2)	Uncommon
General disorders and administration site conditions				
Fatigue[g]	265 (50.5)	Very common	39 (7.4)	Common
Investigations				
Liver laboratory test abnormalities[b]	265 (50.5)	Very common	153 (29.1)	Very common
Blood creatinine increased	93 (17.7)	Very common	0	
Electrocardiogram QT prolonged	34 (6.5)	Common	4 (0.8)	Uncommon
Lipase increased	24 (4.6)	Common	16 (3.0)	Common
Amylase increased	24 (4.6)	Common	10 (1.9)	Common

[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

[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 Renal Failure Acute and Renal Failure

[l] Renal Impairment includes PTs of Azotaemia and Renal Impairment

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

DOSAGE AND ADMINISTRATION

The recommended dose of ZYKADIA is 750 mg taken orally once daily at the same time each day. Continue treatment as long as the patient is deriving clinical benefit from therapy. The maximum recommended dose is 750 mg daily.

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

If Zykadia is taken with a meal, systemic exposure ma exceed that of the same dose taken in the fasted state, and may increase adverse drug reactions. The maximum dose administered in the clinical development program was 750 mg and consumption of food with this dose will increase systemic exposure beyond that investigated for safety and efficacy, and the risks are unknown (see Pharmacokinetics; Absorption, Boxed Warning and Interactions with Other Medicines).

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

DOSAGE ADJUSTMENT

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

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

ZYKADIA should be discontinued for patients unable to tolerate 300 mg daily.

Table 4 summarizes recommendations for dose interruption, reduction, or discontinuation of ZYKADIA in the management of select adverse drug reactions (ADRs).

Table 4 ZYKADIA dose adjustment and management recommendations for adverse drug reactions

Criteria	**ZYKADIA Dosing**
Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation greater than 5 times upper limit of normal (ULN) with total bilirubin less than or equal to 2.0 times ULN	Withhold ZYKADIA until recovery to baseline or less than or equal to 3 times ULN, then reinitiate ZYKADIA by reducing dose by one decrement
ALT or AST elevation greater than 3 times ULN with concurrent total bilirubin elevation greater	Permanently discontinue ZYKADIA

Criteria	ZYKADIA Dosing
than 2.0 times ULN (in the absence of cholestasis or hemolysis)	
Any Grade treatment-related pneumonitis	Permanently discontinue ZYKADIA
QTc greater than 500 msec on at least 2 separate electrocardiograms (ECGs)	Withhold ZYKADIA until recovery to baseline or to a QTc less than 481 msec, then reinitiate ZYKADIA by reducing dose by one decrement
QTc greater than 500 msec or greater than 60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue ZYKADIA
Bradycardia[a] (symptomatic, may be severe and medically significant, medical intervention indicated)	Withhold ZYKADIA until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications If contributing concomitant medication is identified and discontinued, or its dose is adjusted, reinitiate ZYKADIA at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, reinitiate ZYKADIA by reducing dose by one decrement upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above
Bradycardia[a] (life-threatening consequences, urgent intervention indicated)	Permanently discontinue ZYKADIA if no contributing concomitant medication is identified If contributing concomitant medication is identified and discontinued, or its dose is adjusted, reinitiate ZYKADIA by reducing dose by two decrements upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring[b]
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 one decrement
Persistent hyperglycemia greater than 13.9 mmol/ L despite optimal anti-hyperglycemic therapy	Withhold ZYKADIA until hyperglycemia is adequately controlled, then reinitiate ZYKADIA by reducing dose by one decrement 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	Withhold ZYKADIA until lipase or amylase returns to less than or equal to grade 1, then reinitiate by reducing dose by one decrement
[a] *Heart rate less than 60 beats per minutes (bpm)* [b] *Permanently discontinue for recurrence*	

Avoid concurrent use of strong CYP3A inhibitors during treatment with ZYKADIA (see Interactions with other Medicines). If concomitant use of a strong CYP3A inhibitor is

unavoidable, reduce the ZYKADIA dose by approximately one-third, rounded to the nearest multiple of the 150 mg dosage strength. Patients should be carefully monitored for safety. If long-term concomitant treatment with a strong CYP3A inhibitor is necessary and the patient tolerates the reduced dose well, the dose may be increased again with careful monitoring for safety, to avoid potential under-treatment. After discontinuation of a strong CYP3A inhibitor, resume the ZYKADIA dose that was taken prior to initiating the strong CYP3A4 inhibitor.

Patients with renal impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment. Caution should be used in patients with severe renal impairment as there is no experience with ZYKADIA in this population (see Pharmacokinetics; Special Populations).

Patients with hepatic impairment
A dedicated pharmacokinetic study in patients with hepatic impairment has not been conducted. Based on available data, ceritinib is eliminated primarily via the liver. No dose adjustment is necessary in patients with mild hepatic impairment. Ceritinib is not recommended in patients with moderate to severe hepatic impairment (see Pharmacokinetics; Special Populations and Precautions).

Paediatric patients
The safety and efficacy of ZYKADIA have not been established in paediatric patients.

Elderly patients (≥65 years)
The limited data on the safety and efficacy of ZYKADIA in patients aged 65 years and older do not suggest that a dose adjustment is required in elderly patients (see Pharmacokinetics; Special Populations.

OVERDOSE

There is no reported experience with overdose in humans. General supportive measures should be initiated in all cases of overdose. For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

ZYKADIA ceritinib 150 mg hard capsules are opaque white and opaque blue capsule. The opaque blue cap is marked with black ink “LDK 150MG” and the opaque white body is marked with black ink “NVR”. The capsule contains a white to almost white powder.

The blister packaging is made from PCTFE/PVC backed with a heat sealable lacquered aluminium foil. One blister strip contains 10 hard capsules. Multipacks containing 150 (3 packs of 50) hard capsules.

ZYKADIA 150 mg capsules should be stored below 30 °C. Store in original container.

NAME AND ADDRESS OF THE SPONSOR

Novartis Pharmaceuticals Australia Pty Ltd

54 Waterloo Road

Macquarie Park, 2113 NSW

Australia

POISON SCHEDULE OF THE MEDICINE

(S4) Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

31 March 2016

DATE OF MOST RECENT AMENDMENT

06 October 2017

® = Registered Trademark

Internal Document Code: zyk061017i based on CDS 31 March 2016