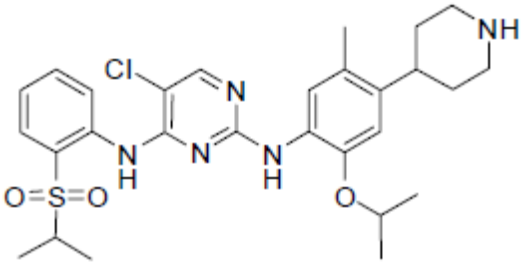
PRODUCT INFORMATION

ZYKADIA®

Ceritinib

SERIOUS ADVERSE EVENTS
The following severe adverse event has 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)



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 a single oral administration in patients under fasted conditions. 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%.

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.

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.

In a dose optimisation study A2112 (ASCEND-8) in patients receiving ZYKADIA 450 mg or 600 mg daily with food (approximately 100 to 500 calories and 1.5 to 15 grams of fat) or 750 mg daily under fasted conditions, there was no clinically meaningful difference in the systemic steady-state exposure of ceritinib (AUC) for the 450 mg with food arm (n=36) compared to the 750 mg fasted arm (n=31). The steady-state AUC increased by 24% and Cmax increased by 25% in the 600 mg with food arm (n=30) compared to the 750 mg fasted arm (n=31).

After a single oral administration of ceritinib in patients, plasma exposure to ceritinib, as represented by C_{max} and AUC_{last}, increased dose-proportionally over 50 to 750 mg under fasting

conditions. In contrast with single-dose data, pre-dose concentration (C_{min}) after repeated daily dosing under fasting conditions 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 under fasted conditions, ceritinib was the main circulating component in human plasma. A total of 11 metabolites were found circulating in plasma at low levels with mean contribution to the radioactivity AUC of ≤2.3% for each metabolite. Main biotransformation pathways identified in healthy subjects included mono-oxygenation, O-dealkylation, and N-formylation. Secondary biotransformation pathways involving the primary biotransformation products included glucuronidation and dehydrogenation. Addition of a thiol group to O-dealkylated ceritinib was also observed.

Elimination

Following single oral doses of ceritinib under fasted conditions, 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. 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

Following a single 750 mg ZYKADIA dose under fasted conditions, the geometric mean systemic exposure (AUCinf) of ceritinib was increased by 66% and unbound ceritinib AUCinf was increased by 108% in subjects with severe (Child-Pugh C) hepatic impairment compared to healthy subjects with normal hepatic function (see Dosage and Administration). 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.

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 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, suggesting that no dose adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment (CrCl <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 7 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 in 925 patients treated with ceritinib 750 mg once daily under fasted conditions. A categorical outlier analysis of ECG data demonstrated new QTc >500 msec in 12 patients (1.3%). There were 58 patients (6.3%) with a QTc increase from baseline >60 msec. A central tendency analysis of the QTc data at average steady-state concentrations from a global phase 3 study (A2301) demonstrated that the upper bound of the 2-sided 90% CI for QTc was 15.3 msec at ceritinib 750 mg once daily under fasted conditions. A pharmacokinetic/pharmacodynamic analysis suggested that ceritinib causes concentration-dependent increases in QTc (see Boxed Warning, Precautions, Adverse Effects, Dosage and Administration).

CLINICAL TRIALS

Previously untreated ALK-positive locally advanced or metastatic NSCLC

The efficacy and safety of ZYKADIA for the treatment of patients with locally advanced or metastatic ALK-positive NSCLC who have not received previous systemic anti-cancer therapy for their metastatic disease was demonstrated in an open-label, randomised, active-controlled, multicentre study (ASCEND-4/Study A2301). Patients were required to have ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx Assay. Neurologically stable patients with central nervous system (CNS) metastases that did not require increasing doses of steroids to manage CNS symptoms were permitted to enrol.

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 Tumours (RECIST 1.1). Additional efficacy endpoints included overall survival (OS), overall response rate (ORR), duration of response (DOR), disease control rate (DCR), time to response (TTR) and patient reported outcomes.

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

Patients were randomised 1:1 to receive ZYKADIA 750 mg orally once daily under fasted conditions or chemotherapy plus maintenance chemotherapy. Randomisation was stratified by World Health Organization (WHO) performance status, prior adjuvant/neoadjuvant chemotherapy and presence or absence of CNS metastases. Patients randomised to chemotherapy received pemetrexed (500 mg/m^2) and investigator's choice of cisplatin (75 mg/m^2) or carboplatin (AUC of 5 - 6 mg*min/mL) administered on day 1 of each 21-day cycle for a maximum of 4 cycles followed by pemetrexed (500 mg/m^2) every 21 days. Treatment in both arms was continued until disease progression or unacceptable toxicity. Patients randomised to the chemotherapy arm could crossover to receive ZYKADIA upon RECIST-defined disease progression by BIRC.

A total of 376 patients were randomised to receive ZYKADIA (n=189) or chemotherapy (n=187). The demographic characteristics of the study population were 57% female, median age 54 years (range: 22 to 81 years), 22% age 65 years or older, 54% Caucasian, 42% Asian, 2% Black, and 2% other races. The WHO performance status was 0/1/2 in 37%/56%/6% of patients respectively. The majority of patients had adenocarcinoma (97%) and never smoked (61%). CNS metastases were present in 32% (n=121) of patients. Approximately half (n=55) had measurable CNS metastases as determined by BIRC neuro-radiologist and 71% (n=39) of these patients received no prior intracranial radiotherapy. Of those randomised to chemotherapy, 43% received ZYKADIA as the next antineoplastic therapy after platinum-based chemotherapy.

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

Efficacy data from Study A2301 are summarised in Table 1 and the Kaplan-Meier curves for PFS is shown in Figure 1.

Table 1 ASCEND-4 (Study A2301) - Efficacy results in patients with previously untreated ALK-positive locally advanced or metastatic NSCLC

	Zykadia (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	
Tumour 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; NE=not estimable; CR=complete response; PR=partial response

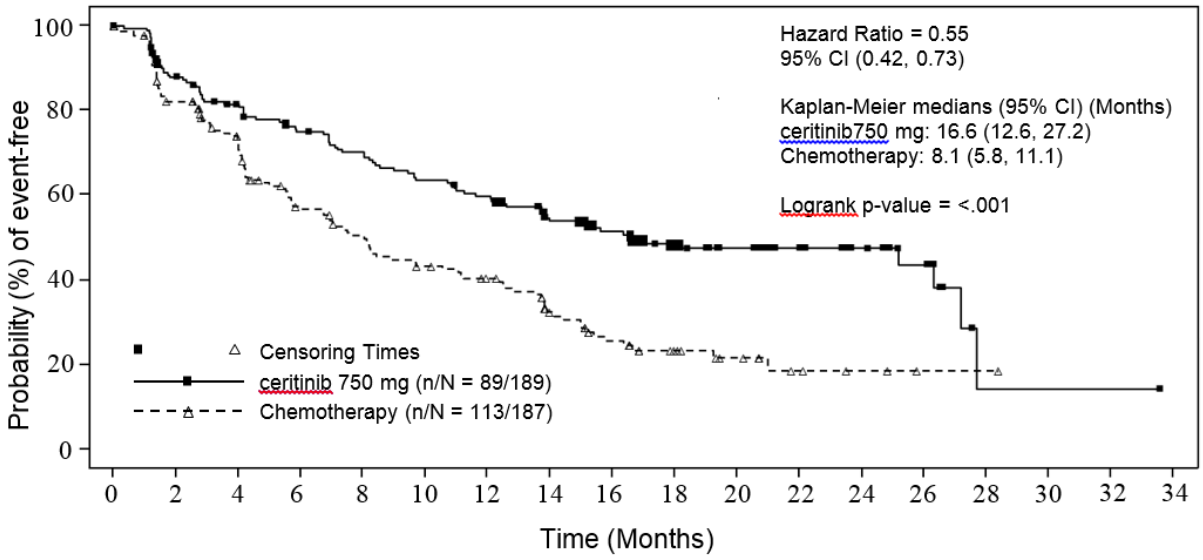
[a] *Based on the Cox proportional hazards stratified analysis.*

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

[c] *OS analysis was not adjusted for the effects of cross over.*

[d] *Estimated using the Kaplan-Meier method.*

Figure 1 **ASCEND-4 (Study A2301) - Kaplan-Meier plot of progression-free survival as assessed by BIRC**



	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
LDK378 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

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

Analyses of patient-reported outcome measures suggested ceritinib prolonged time to deterioration for the lung cancer specific symptoms cough, pain and dyspnoea compared to chemotherapy. The patient-reported delay to deterioration may be an overestimation, because patients were not blinded to treatment assignment.

Anti-tumour activity of ZYKADIA in the brain was assessed in patients with measurable disease at baseline with at least one post baseline assessment as determined by the BIRC neuro-radiologist at baseline (N=44) according to RECIST 1.1 (see Table 2).

Table 2 BIRC assessed CNS responses in patients with measurable CNS lesions with at least one post baseline assessment in ASCEND-4

	ZYKADIA	Chemotherapy
Intracranial Tumor Response Assessment	N=22	N=22
Overall intracranial response rate, % (95% CI)[a]	72.7% (49.8, 89.3)	27.3% (10.7, 50.2)
Complete response, %	9.1%	9.1%
Partial response, %	63.6%	18.2%
Intracranial Disease Control Rate, % (95% CI)[a]	86.4% (65.1, 97.1)	90.9% (70.8, 98.9)
Duration of Intracranial Response		
Number of responders	N=16	N=6
Median in months (95% CI)	16.6 (8.1, NE)	NE (1.5, NE)

[a]Clopper and Pearson exact binomial 95% confidence interval
BIRC: Blinded independent review committee; **CI:** Confidence Interval; **NE:** Not Estimable

Previously treated ALK-positive locally advanced or metastatic NSCLC

The efficacy and safety of ZYKADIA for the treatment of patients with locally advanced or metastatic ALK-positive NSCLC, who have received previous treatment with crizotinib was demonstrated in an open-label, randomised, active-controlled, multicentre study (ASCEND-5/Study A2303). Patients were required to have ALK-positive NSCLC as identified by the VYSIS ALK Break Apart FISH test. Neurologically stable patients with CNS metastases that did not require increasing doses of steroids to manage CNS symptoms were permitted to enrol.

The primary efficacy endpoint was PFS, as determined by BIRC, according to RECIST 1.1. Additional efficacy endpoints included OS, ORR, DOR, DCR, TTR and patient reported outcomes.

OIRR, IDCR and DOIR were determined by BIRC neuro-radiologist per modified RECIST 1.1 (i.e. up to 5 lesions in the brain).

Patients were randomised 1:1 to receive ZYKADIA 750 mg orally once daily under fasted conditions or chemotherapy. Randomisation was stratified by WHO performance status and presence or absence of CNS metastases. Patients randomised to chemotherapy received investigator's choice of pemetrexed (500 mg/m^2) or docetaxel (75 mg/m^2) administered on day 1 of each 21-day cycle. Treatment in both arms was continued until disease progression or unacceptable toxicity. Patients randomised to the chemotherapy arm could crossover to receive ZYKADIA upon RECIST-defined disease progression by BIRC.

A total of 231 patients were randomised to receive ZYKADIA (n=115) or chemotherapy (n=116); in the chemotherapy arm, 73 patients received docetaxel and 40 received pemetrexed.

The demographic characteristics of the study population were 56% female, median age 54 years (range: 28 to 84 years), 23% age 65 years or older, 65% Caucasian, 29% Asian, <1% Black, and 3% other races. The WHO performance status was 0/1/2 in 46%/48%/6% of patients respectively, and 58% had CNS metastasis at baseline.

All patients had been treated previously with crizotinib, and in 82% of both arms it was their most recent treatment). All except one patient had received prior chemotherapy (including a platinum doublet) for advanced disease; 11% of the patients in the ZYKADIA arm and 12% of the patients in the chemotherapy arm had received two prior chemotherapy regimens for advanced disease.

The median duration of follow-up was 16.5 months.

Efficacy data from Study A2303 are summarised in Table 3 and the Kaplan-Meier curve for PFS in Figure 2.

Table 3 ASCEND-5 (Study A2303) – Efficacy result in patients with previously treated ALK-positive locally advanced or metastatic NSCLC

	Zykadia (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	
Overall survival[c]		
Number of events, n (%)	48 (41.7%)	50 (43.1%)
Median, months (95% CI)	18.1 (13.4, 23.9)	20.1 (11.9, 25.1)
HR (95% CI)[a]	1.00 (0.67,1.49)	
p-value[b]	0.496	
Tumour 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[d] (95% CI)	6.9 (5.4, 8.9)	8.3 (3.5, NE)
Event-free probability estimate at 9 months[d] (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.*

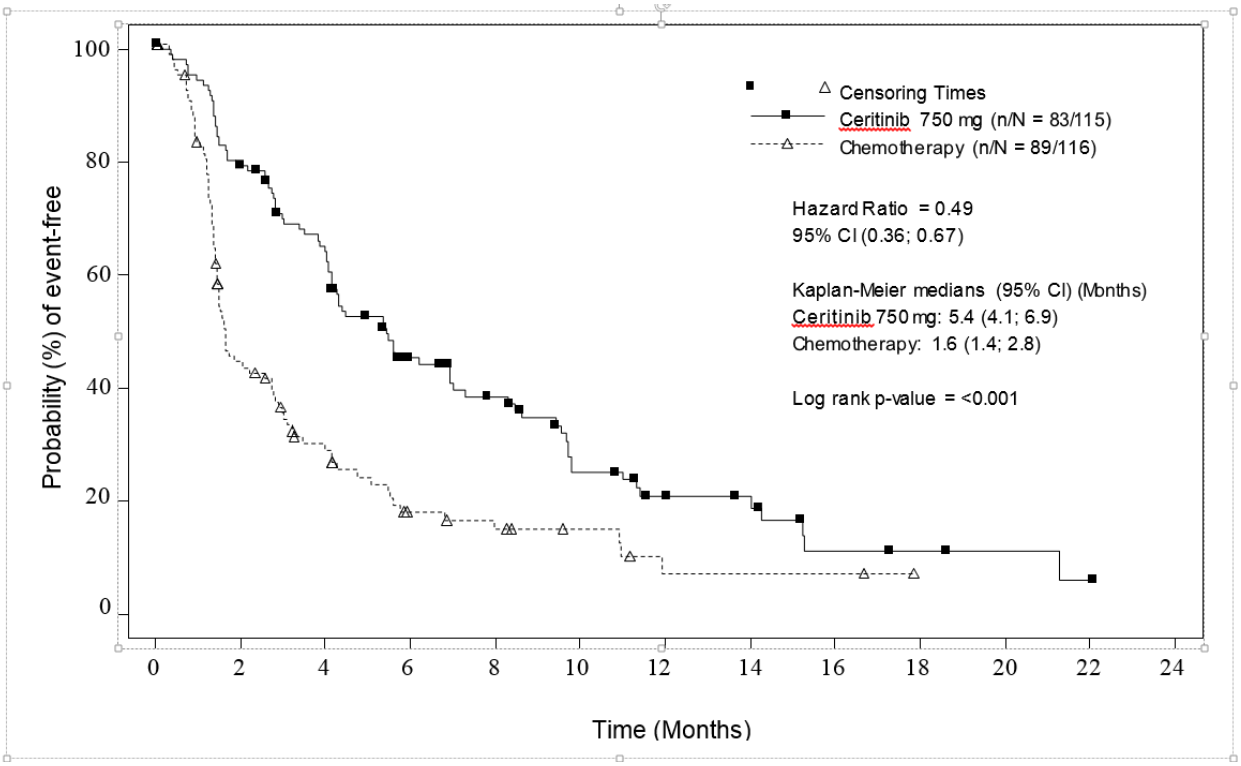
[b] *Based on the stratified log-rank test.*

[c] *OS analysis was not adjusted for the effects of cross over.*

[d] *Estimated using the Kaplan-Meier method.*

There was no significant difference in OS in a pre-specified interim analysis conducted at approximately 50% of the events required for the final analysis.

Figure 2 **ASCEND-5 (Study A2303) - Kaplan-Meier plot of progression-free survival as assessed by BIRC**



	No. of patients still at risk												
Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24
LDK378 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

Analyses of patient-reported outcome measures suggested ceritinib prolonged time to deterioration for the lung cancer specific symptoms cough, pain and dyspnoea compared to chemotherapy. The patient-reported delay to deterioration may be an overestimation, because patients were not blinded to treatment assignment.

Anti-tumour activity of ZYKADIA in the brain was assessed in patients with measurable disease at baseline with at least one post baseline assessment as determined by the BIRC neuro-radiologist at baseline (N=37) according to RECIST 1.1. (see Table 4).

Table 4 BIRC Assessed CNS Responses in Patients with Measurable CNS Lesions with at least one post baseline assessment in ASCEND-5

	ZYKADIA	Chemotherapy
Intracranial Tumor Response Assessment	N=17	N=20
Overall intracranial response rate, % (95% CI)[a]	35.3% (14.2, 61.7)	5.0% (0.1, 24.9)
Complete response, %	0%	0.0%
Partial response, %	35.3%	5.0%
Intracranial Disease Control Rate, % (95% CI)[a]	76.5% (50.1, 93.2)	60.0% (36.1,80.9)
Duration of Intracranial Response		
Number of responders	n=6	n=1
Median in months (95% CI)	6.9 (2.7, 8.3)	NE

[a]Clopper and Pearson exact binomial 95% confidence interval
BIRC: Blinded independent review committee; **CI:** Confidence Interval; **NE:** Not Estimable

INDICATIONS

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

CONTRAINDICATIONS

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

PRECAUTIONS

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

HEPATOTOXICITY

Drug-induced hepatotoxicity occurred in patients treated with ZYKADIA. Elevations in alanine aminotransferase (ALT) greater than 5 times the upper limit of normal (ULN) occurred in 28% and elevations in aspartate aminotransferase (AST) greater than 5 times ULN occurred in 16% of 925 patients across clinical studies. Concurrent elevations in ALT greater than 3 times the ULN and total bilirubin greater than 2 times the ULN, with alkaline phosphatase less than 2 times the

ULN occurred in 0.3% of patients across clinical studies. Approximately 1.0% of patients required permanent discontinuation due to hepatotoxicity.

Monitor with liver laboratory tests including ALT, AST, and total bilirubin once a month and as clinically indicated, with more frequent testing in patients who develop transaminase elevations. Based on the severity of the adverse drug reaction, withhold ZYKADIA with resumption at a reduced dose, or permanently discontinue ZYKADIA as described in Table 8 (see Dosage and Administration and Adverse Effects).

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, ILD events (including 'pneumonitis', 'ILD', 'Lung Infiltration' and 'Alveolitis Allergic') occurred in 2.4% of patients, and in 1.3% these were grade 3 or 4. ILD events that required dose reduction/interruptions were reported in 1.2% and those that led to discontinuation were reported in 1.1%. 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, 9.7% of patients treated with ZYKADIA had events of QT prolongation (any grade), including grade 3 or 4 events in 2.1% of patients. These events required dose reduction or interruption in 2.1% of patients and led to discontinuation in 0.2% of patients.

A categorical outlier analysis of ECG 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 indicates 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 ZYKADIA 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 150 mg (see Dosage and Administration, Adverse Events and Pharmacokinetics; Special Population).

BRADYCARDIA

In clinical studies, events of bradycardia and sinus bradycardia were reported in 1.2% and 1.1% of patients respectively, with 0.2% requiring dose adjustment or interruption for bradycardia, but none requiring treatment discontinuation. Asymptomatic cases of bradycardia have been observed in 11 out of 925 (1.2%) 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 150 mg 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 ADVERSE REACTIONS

In clinical studies, gastrointestinal adverse reactions (all grades) occurred in 94.8% of patients treated at a dose of 750 mg under fasted conditions. Diarrhoea, nausea and vomiting occurred in 82.1%, 74.7% and 63.2% 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 5.2%, 5.3% and 5.6% of patients, respectively. Nausea led to dose discontinuation in 5 patients (0.5%) and nausea and vomiting led to dose discontinuation in 7 patients (0.8%). Nausea, vomiting, and diarrhoea led to dose adjustments or interruptions in 16.8%, 19.2%, and 15.0%, respectively.

Gastrointestinal events were managed primarily with concomitant medicinal products including anti-emetic/anti-diarrhoeal medicinal products (in 81.0% of patients) and/or with dose reduction or interruption (in 32.2% of patients). Gastrointestinal events led to discontinuation in 0.6% of patients.

Diarrhoea, nausea, or vomiting occurred in 74.2% of 89 patients treated with ZYKADIA at the recommended dose of 450 mg taken with food in a dose optimisation study A2112 (ASCEND-8) and were mainly grade 1 events (49.4%). One patient (1.1%) experienced grade 3 diarrhoea. Seven patients (7.9%) required study drug interruption due to diarrhoea or nausea. No patients required

dose reduction or discontinuation of ZYKADIA due to diarrhoea, nausea, or vomiting (see Adverse Events).

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

Hyperglycaemia occurred in patients receiving ZYKADIA. Across clinical studies, hyperglycaemia AEs occurred in 13% of which CTCAE Grade 3 or 4 hyperglycaemia AEs occurred in 6.5% of 925 patients. Monitor fasting serum glucose prior to the start of ZYKADIA treatment and periodically thereafter as clinically indicated. Initiate or optimise anti-hyperglycaemic medications as indicated. Based on the severity of the adverse drug reaction withhold ZYKADIA until hyperglycaemia is adequately controlled, then resume ZYKADIA at a reduced dose as described in Table 8. If adequate hyperglycaemic control cannot be achieved with optimal medical management, permanently discontinue ZYKADIA (see Dosage and Administration and Adverse Events).

PANCREATIC TOXICITY

Pancreatitis occurred in patients receiving ZYKADIA. Pancreatitis, including one fatality, occurred in less than 1% of patients receiving ZYKADIA in clinical studies. CTCAE Grade 3 or 4 elevations of amylase occurred in 7 % of patients receiving ZYKADIA across clinical studies. CTCAE Grade 3 or 4 elevations of lipase occurred in 14 % of patients. Monitor lipase and amylase prior to the start of ZYKADIA treatment and periodically thereafter as clinically indicated. Based on the severity of the laboratory abnormalities, withhold ZYKADIA with resumption at a reduced dose as described in Table 8 (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 seven clinical studies, 168 of 925 patients (18.2%) 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 fasted 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 under fasted conditions 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 ceritinib under fasted conditions 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 a dose of 750 mg daily under fasted conditions may exceed the Ki values for the inhibition of CYP3A and CYP2C9 suggesting that ceritinib could inhibit the clearance of other medicinal products metabolised by these enzymes at clinically relevant concentrations. Dose reduction may be needed for co-administered medicines that are predominantly metabolised 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 metabolised 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

ZYKADIA should be taken with food. The bioavailability of ceritinib is increased in the presence of food (see Pharmacokinetics; Absorption). 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

Summary of the safety profile

The data described below reflect exposure to ZYKADIA 750 mg orally once daily fasted in 925 patients with ALK-positive advanced NSCLC in seven clinical studies including two randomised, active controlled, phase 3 studies (A2301 and A2303).

The median duration of exposure to ZYKADIA 750 mg under fasted conditions was 44.9 weeks (range 0.1 to 200.1 weeks). Dose reductions occurred in 62.2% of patients and dose interruptions in 74.8% of patients.

The rate of adverse events (AEs) resulting in permanent discontinuation of ZYKADIA was 12.1%. The most frequent AEs (>0.5%) leading to discontinuation of ZYKADIA were pneumonia (0.6%) and respiratory failure (0.6%).

The most frequently(>10%) reported AEs for study A2301 regardless of study drug relationship in either treatment group are reported in Table 5 below.

Table 5 Study A2301 adverse events (greater than 10% for all grades in either treatment group) (Safety set)

	Zykadia 750 mg (fasted) N=189		**Chemotherapy N=175**	
Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
-Total	189 (100)	148 (78.3)	170 (97.1)	108 (61.7)
Diarrhoea	160 (84.7)	10 (5.3)	19 (10.9)	2 (1.1)
Nausea	130 (68.8)	5 (2.6)	97 (55.4)	9 (5.1)
Vomiting	125 (66.1)	10 (5.3)	63 (36.0)	10 (5.7)
Alanine Aminotransferase Increased	114 (60.3)	58 (30.7)	38 (21.7)	5 (2.9)
Aspartate Aminotransferase Increased	100 (52.9)	32 (16.9)	34 (19.4)	3 (1.7)
Gamma-Glutamyltransferase Increased	70 (37.0)	54 (28.6)	18 (10.3)	3 (1.7)
Decreased Appetite	64 (33.9)	2 (1.1)	55 (31.4)	2 (1.1)
Blood Alkaline Phosphatase Increased	55 (29.1)	14 (7.4)	8 (4.6)	1 (0.6)
Fatigue	55 (29.1)	8 (4.2)	52 (29.7)	5 (2.9)
Abdominal Pain	47 (24.9)	4 (2.1)	13 (7.4)	0
Cough	46 (24.3)	0	28 (16.0)	0
Weight Decreased	45 (23.8)	7 (3.7)	26 (14.9)	1 (0.6)
Blood Creatinine Increased	42 (22.2)	4 (2.1)	17 (9.7)	0
Abdominal Pain Upper	39 (20.6)	3 (1.6)	10 (5.7)	0
Non-Cardiac Chest Pain	38 (20.1)	2 (1.1)	17 (9.7)	1 (0.6)
Back Pain	36 (19.0)	3 (1.6)	32 (18.3)	4 (2.3)
Constipation	36 (19.0)	0	38 (21.7)	0
Pyrexia	34 (18.0)	0	24 (13.7)	2 (1.1)
Asthenia	33 (17.5)	5 (2.6)	36 (20.6)	6 (3.4)

Headache	31 (16.4)	0	21 (12.0)	2 (1.1)
Dyspnoea	29 (15.3)	4 (2.1)	35 (20.0)	11 (6.3)
Anaemia	28 (14.8)	4 (2.1)	62 (35.4)	13 (7.4)
Rash	28 (14.8)	1 (0.5)	11 (6.3)	1 (0.6)
Dizziness	22 (11.6)	2 (1.1)	17 (9.7)	1 (0.6)
Electrocardiogram QT Prolonged	21 (11.1)	4 (2.1)	2 (1.1)	1 (0.6)
Hyperglycaemia	21 (11.1)	12 (6.3)	13 (7.4)	5 (2.9)
Musculoskeletal Pain	21 (11.1)	1 (0.5)	11 (6.3)	1 (0.6)
Pain In Extremity	21 (11.1)	0	13 (7.4)	0
Amylase Increased	19 (10.1)	9 (4.8)	9 (5.1)	3 (1.7)
Pruritus	19 (10.1)	1 (0.5)	8 (4.6)	0
Oedema Peripheral	10 (5.3)	0	26 (14.9)	1 (0.6)
Stomatitis	10 (5.3)	1 (0.5)	19 (10.9)	0
Neutropenia	9 (4.8)	1 (0.5)	38 (21.7)	19 (10.9)
White Blood Cell Count Decreased	7 (3.7)	0	31 (17.7)	7 (4.0)
Neutrophil Count Decreased	5 (2.6)	2 (1.1)	26 (14.9)	9 (5.1)
Thrombocytopenia	3 (1.6)	1 (0.5)	18 (10.3)	6 (3.4)

The most frequently (>10%) reported AEs for study A2303 regardless of study drug relationship in either treatment group are reported in Table 6 below.

Table 6 Study A2303 adverse events (greater than 10% for all grades in either groups) (Safety Set)

	Zykadia N=115		**Chemotherapy N=113**		**Pemetrexed N=40**		**Docetaxel N=73**	
	All grades	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
-Total	115 (100)	89 (77.4)	112 (99.1)	72 (63.7)	40 (100)	18 (45.0)	72 (98.6)	54 (74.0)
Diarrhoea	83 (72.2)	5 (4.3)	20 (17.7)	1 (0.9)	1 (2.5)	0	19 (26.0)	1 (1.4)
Nausea	76 (66.1)	9 (7.8)	26 (23.0)	2 (1.8)	14 (35.0)	1 (2.5)	12 (16.4)	1 (1.4)
Vomiting	60 (52.2)	9 (7.8)	6 (5.3)	1 (0.9)	2 (5.0)	1 (2.5)	4 (5.5)	0
ALT increased	49 (42.6)	24 (20.9)	10 (8.8)	2 (1.8)	8 (20.0)	2 (5.0)	2 (2.7)	0
Decreased appetite	48 (41.7)	2 (1.7)	22 (19.5)	3 (2.7)	5 (12.5)	0	17 (23.3)	3 (4.1)
AST increased	42 (36.5)	16 (13.9)	5 (4.4)	1 (0.9)	3 (7.5)	1 (2.5)	2 (2.7)	0
Weight decreased	34 (29.6)	3 (2.6)	7 (6.2)	1 (0.9)	1 (2.5)	0	6 (8.2)	1 (1.4)
Fatigue	31 (27.0)	6 (5.2)	32 (28.3)	5 (4.4)	14 (35.0)	2 (5.0)	18 (24.7)	3 (4.1)
Asthenia	26 (22.6)	6 (5.2)	21 (18.6)	7 (6.2)	8 (20.0)	4 (10.0)	13 (17.8)	3 (4.1)
Blood ALP increased	26 (22.6)	7 (6.1)	1 (0.9)	0	0	0	1 (1.4)	0
GGT increased	26 (22.6)	24 (20.9)	2 (1.8)	1 (0.9)	0	0	2 (2.7)	1 (1.4)
Abdominal pain	25 (21.7)	1 (0.9)	11 (9.7)	1 (0.9)	5 (12.5)	0	6 (8.2)	1 (1.4)
Back pain	25 (21.7)	1 (0.9)	8 (7.1)	3 (2.7)	3 (7.5)	1 (2.5)	5 (6.8)	2 (2.7)
Blood creatinine increased	22 (19.1)	0	0	0	0	0	0	0
Constipation	22 (19.1)	0	15 (13.3)	0	6 (15.0)	0	9 (12.3)	0
Headache	22 (19.1)	1 (0.9)	17 (15.0)	2 (1.8)	6 (15.0)	1 (2.5)	11 (15.1)	1 (1.4)
Dyspnoea	20 (17.4)	6 (5.2)	21 (18.6)	7 (6.2)	7 (17.5)	2 (5.0)	14 (19.2)	5 (6.8)

Pyrexia	19 (16.5)	2 (1.7)	17 (15.0)	0	4 (10.0)	0	13 (17.8)	0
Abdominal pain upper	18 (15.7)	1 (0.9)	5 (4.4)	0	1 (2.5)	0	4 (5.5)	0
Cough	16 (13.9)	0	18 (15.9)	1 (0.9)	6 (15.0)	0	12 (16.4)	1 (1.4)
Non-cardiac chest pain	15 (13.0)	1 (0.9)	4 (3.5)	0	2 (5.0)	0	2 (2.7)	0
Electrocardiogram QT prolonged	13 (11.3)	1 (0.9)	0	0	0	0	0	0
Rash	13 (11.3)	0	12 (10.6)	0	6 (15.0)	0	6 (8.2)	0
Arthralgia	12 (10.4)	0	13 (11.5)	3 (2.7)	3 (7.5)	2 (5.0)	10 (13.7)	1 (1.4)
Nasopharyngitis	12 (10.4)	0	1 (0.9)	0	1 (2.5)	0	0	0
Alopecia	6 (5.2)	0	24 (21.2)	0	1 (2.5)	0	23 (31.5)	0
Anaemia	6 (5.2)	0	19 (16.8)	5 (4.4)	5 (12.5)	4 (10.0)	14 (19.2)	1 (1.4)
Stomatitis	5 (4.3)	0	15 (13.3)	0	6 (15.0)	0	9 (12.3)	0
Myalgia	4 (3.5)	0	13 (11.5)	0	2 (5.0)	0	11 (15.1)	0
Neutropenia	4 (3.5)	1 (0.9)	23 (20.4)	17 (15.0)	3 (7.5)	0	20 (27.4)	17 (23.3)
ALT=alanine aminotransferase; ALP=alkaline phosphatase, AST=aspartate aminotransferase; GGT=gamma-glutamyltransferase								

Adverse Drug Reactions (ADR)

Adverse drug reactions (ADRs) with an incidence of ≥10% in patients treated with ZYKADIA 750 mg fasted were diarrhoea, nausea, vomiting, fatigue, liver laboratory test abnormalities, abdominal pain, decreased appetite, weight decreased, constipation, rash, blood creatinine increased, oesophageal disorder and anaemia.

Grade 3/4 ADRs with an incidence of ≥5% in patients treated with ZYKADIA 750 mg fasted were liver laboratory test abnormalities, fatigue, vomiting, diarrhoea, nausea and hyperglycaemia.

Table 7 presents the frequency category of ADRs reported for ZYKADIA in patients treated at a dose of 750 mg under fasted conditions (n=925) in 7 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 7 Adverse drug reactions in patients (n=925) 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	141 (15.2)	Very common	28 (3.0)	Common
Metabolism and nutrition disorders				
Decreased appetite	365 (39.5)	Very common	20 (2.2)	Common
Hyperglycemia	87 (9.4)	Common	50 (5.4)	Common
Hypophosphatemia	49 (5.3)	Common	21 (2.3)	Common
Eye disorders				
Vision disorder[m]	65 (7.0)	Common	0	
Cardiac disorders				
Pericarditis[h]	54 (5.8)	Common	24 (2.6)	Common
Bradycardia[e]	21 (2.3)	Common	0	
Respiratory, thoracic and mediastinal disorders				
Pneumonitis[i]	19 (2.1)	Common	11 (1.2)	Common
Gastrointestinal disorders**				
Diarrhea	759 (82.1)	Very common	48 (5.2)	Common
Nausea	691 (74.7)	Very common	49 (5.3)	Common
Vomiting	585 (63.2)	Very common	52 (5.6)	Common
Abdominal pain[a]	426 (46.1)	Very common	23 (2.5)	Common
Constipation	222 (24.0)	Very common	3 (0.3)	Uncommon
Esophageal disorder[f]	130 (14.1)	Very common	4 (0.4)	Uncommon
Pancreatitis	5 (0.5)	Uncommon	5 (0.5)	Uncommon
Hepatobiliary disorders				
Abnormal liver function tests[c]	20 (2.2)	Common	9 (1.0)	Common
Hepatotoxicity[d]	10 (1.1)	Common	4 (0.4)	Uncommon
Skin and subcutaneous tissue disorders				
Rash[j]	181 (19.6)	Very common	4 (0.4)	Uncommon
Renal and urinary disorders				
Renal failure[k]	17 (1.8)	Common	2 (0.2)	Uncommon
Renal impairment[l]	9 (1.0)	Common	1 (0.1)	Uncommon
General disorders and administration site conditions				
Fatigue[g]	448 (48.4)	Very common	71 (7.7)	Common
Investigations				
Liver laboratory test abnormalities[b]	560 (60.5)	Very common	347 (37.5)	Very common
Weight decreased	255 (27.6)	Very common	26 (2.8)	Common
Blood creatinine increased	204 (22.1)	Very common	5 (0.5)	Uncommon
Electrocardiogram QT prolonged	90 (9.7)	Common	19 (2.1)	Common
Lipase increased	44 (4.8)	Common	32 (3.5)	Common
Amylase increased	65 (7.0)	Common	29 (3.1)	Common

Primary System Organ Class Preferred Term	All grades n (%)	Frequency category	Grades 3/4 n (%)	Frequency category
[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] 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* **Study A2201: Phase II, multicenter, single arm study in adult patients with ALK-positive NSCLC previously treated with crizotinib and 1-3 lines of chemotherapy.* **Study AX2101: Phase I (with extension phase), multicenter, dose escalation study in patients with ALK-positive tumours including those who had received prior treatment with chemotherapy (any number of prior chemotherapies) and/or crizotinib.* **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 tumours.* **A2109: Phase 1/II, multicenter, open label, single arm study in adult Chinese patients with ALK-positive advanced NSCLC previously treated with crizotinib with or without chemotherapy.* **A2303 Phase III and *A2301 Phase III: Described in clinical trials section above.* ***For frequency of gastrointestinal adverse reactions at the recommended dose of 450 mg with food, see ASCEND 8 data below.*				

In the dose optimisation 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=89) was consistent with ZYKADIA 750 mg fasted (N=90), except for a reduction in gastrointestinal adverse drug reactions, while achieving comparable steady-state exposure (see Pharmacokinetics). The incidence and severity of gastrointestinal adverse drug reactions (diarrhoea 56%, nausea 45%, vomiting 35%; 1.1% reported a grade 3/4 event) were reduced for patients treated with ZYKADIA 450 mg with food compared to 750 mg fasted (diarrhoea 76%, nausea 50%, vomiting 56%; 12% reported a grade 3/4 event). In patients treated with ZYKADIA 450 mg with food, 10% of patients had at least one adverse event

that required dose reduction and 42% of patients had at least one adverse event that required study drug interruption.

DOSAGE AND ADMINISTRATION

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. Continue treatment as long as the patient is deriving clinical benefit from therapy. The maximum recommended dose is 450 mg taken orally once daily with food.

ZYKADIA capsules should be swallowed whole with water. The capsules should not be chewed or crushed.

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 an adverse drug reaction not listed in Table 8, then the daily dose of ZYKADIA should be reduced by decrements of 150 mg. Early identification and management of adverse drug reactions with standard supportive care measures should be considered.

ZYKADIA should be discontinued in patients unable to tolerate 150 mg taken daily with food.

Table 8 summarises recommendations for dose interruption, reduction, or discontinuation of ZYKADIA in the management of select adverse drug reactions (ADRs).

Table 8 ZYKADIA dose adjustment and management recommendations for adverse drug reactions

Criteria	**ZYKADIA Dosing**
Severe or intolerable nausea, vomiting, or diarrhoea despite optimal anti-emetic or anti-diarrhoeal 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 2 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 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.

Criteria	ZYKADIA Dosing
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.
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 150 mg 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 150 mg upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring[b]
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 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	Withhold ZYKADIA until lipase or amylase returns to less than or equal to grade 1, then reinitiate by reducing dose by 150 mg.
[a] Heart rate less than 60 beats per minute (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 CYP3A 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
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 Pharmacokinetics). No dose adjustment is recommended in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

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

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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

01 August 2018

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