History and Development of Zykadia™ (ceritinib)

1994 Researchers identify anaplastic lymphoma kinase (ALK) as the tyrosine kinase component of a novel fusion gene that results from a chromosomal translocation in anaplastic large-cell lymphoma (ALCL)[1]

2003 Researchers at Novartis begin efforts to develop targeted ALK inhibitors for ALCL

2007 The EML4-ALK translocation is identified in non-small cell lung cancer (NSCLC)[2]

Selective ALK inhibitor activity is first demonstrated in animal models of ALCL[3]

2010 Novartis identifies ceritinib in animal models as a potent and specific inhibitor of ALK

2011 **January:** Ceritinib enters Phase I clinical trials and the first patient is treated

August: The US Food and Drug Administration (FDA) approves the first therapy for ALK+ NSCLC (Xalkori®* [crizotinib])

November: First presented ceritinib data show durable responses in patients with an EML4-ALK xenograft with a crizotinib-resistant mutation (C1156Y)[4]

2012 **April:** Novartis demonstrates Proof of Concept for ceritinib showing that the compound is active in patients with ALK+ NSCLC

June: Novartis presents Phase I data of ceritinib in advanced solid tumors showing preliminary responses in crizotinib-naïve and crizotinib-relapsed patients[5]

November: Novartis initiates large Phase II studies in patients with ALK+NSCLC

2013 **March:** Ceritinib receives Breakthrough Therapy designation from the US FDA

June: Phase I data demonstrate clinical response in 78 patients with ALK+ metastatic NSCLC who had progressed during or after crizotinib therapy or had not been previously treated with crizotinib[6]

June: Novartis initiates large Phase III studies in patients with ALK+NSCLC

September: Novartis initiates expanded treatment protocol for ceritinib in ALK+ NSCLC[7]

December: Ceritinib regulatory application is submitted to the US FDA

2014 **Q1:** Novartis submits European Medicines Agency (EMA) regulatory application for ceritinib

March: Ceritinib Phase I data published in *The New England Journal of Medicine* showed 66 patients with ALK+ NSCLC in the study experienced a clinical response [8]

April: Zykadia is approved by the US FDA for the treatment of patients with ALK+ metastatic NSCLC who have progressed on or are intolerant to crizotinib[9]. This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. This indication addresses an unmet medical need for patients.

Please see indication and Important Safety Information on the next page

About Zykadia
Zykadia (ceritinib) is indicated for the treatment of patients with ALK+ metastatic NSCLC who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Zykadia Important Safety Information
Diarrhea, nausea, vomiting, or abdominal pain occurred in 96% of 255 patients including severe cases in 14% of patients treated with Zykadia in Study 1. Dose modification due to diarrhea, nausea, vomiting, or abdominal pain occurred in 38% of patients. Patients should be monitored and managed using standards of care, including anti-diarrheals, anti-emetics, or fluid replacement, as indicated. Based on the severity of the adverse drug reaction, withhold Zykadia with resumption at a reduced dose as described in Table 1 of the package insert.

Drug-induced hepatotoxicity occurred in patients treated with Zykadia. Elevations in alanine aminotransferase (ALT) greater than 5 times the upper limit of normal (ULN) occurred in 27% of 255 patients in Study 1. One patient (0.4%) required permanent discontinuation due to elevated transaminases and jaundice. Patients should be monitored with liver laboratory tests including ALT, aspartate aminotransferase (AST), and total bilirubin once a month and as clinically indicated, with more frequent testing in patients who develop transaminase elevations. Based on the severity of the adverse drug reaction, withhold Zykadia with resumption at a reduced dose, or permanently discontinue Zykadia as described in Table 1 of the package insert.

Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with Zykadia. In Study 1, pneumonitis was reported in 4% of 255 patients treated with Zykadia. CTCAE Grade 3 or 4 ILD/pneumonitis was reported in 3% of patients, and fatal ILD/pneumonitis was reported in 1 patient (0.4%) in Study 1. One percent (1%) of patients discontinued Zykadia in Study 1 due to ILD/pneumonitis. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. Exclude other potential causes of ILD/pneumonitis, and permanently discontinue Zykadia in patients diagnosed with treatment-related ILD/pneumonitis.

QTc interval prolongation occurs in patients treated with Zykadia. Three percent (3%) of 255 patients experienced a QTc interval increase over baseline greater than 60 msec in Study 1. Across the development program of Zykadia, one of 304 patients (less than 1%) treated with Zykadia doses ranging from 50 to 750 mg was found to have a QTc greater than 500 msec and 3% of patients had an increase from baseline QTc greater than 60 msec. A pharmacokinetic analysis suggested that Zykadia causes concentration-dependent increases in the QTc interval. When possible, avoid use of Zykadia in patients with congenital long QT syndrome. Conduct periodic monitoring with electrocardiograms (ECGs) and electrolytes in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or those who are taking medications that are known to prolong the QTc interval. Withhold Zykadia in patients who develop a QTc interval greater than 500 msec on at least 2 separate ECGs until the QTc interval is less than 481 msec or recovery to baseline if the QTc interval is greater than or equal to 481 msec, then resume Zykadia at a reduced dose as described in Table 1 of the package insert. Permanently discontinue Zykadia in patients who develop QTc interval prolongation in combination with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia.

Hyperglycemia can occur in patients receiving Zykadia. In Study 1, CTCAE Grade 3-4 hyperglycemia, based on laboratory values, occurred in 13% of 255 patients. There was a 6-fold increase in the risk of CTCAE Grade 3-4 hyperglycemia in patients with diabetes or glucose intolerance and a 2-fold increase in patients taking corticosteroids. Monitor serum glucose levels as clinically indicated. Initiate or optimize anti-hyperglycemic medications as indicated. Based on the severity of the adverse drug reaction, withhold Zykadia until hyperglycemia is adequately controlled, then resume Zykadia at a reduced dose as described in Table 1 of the package insert. If adequate hyperglycemic control cannot be achieved with optimal medical management, permanently discontinue Zykadia.

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

as an adverse drug reaction in 3% of patients in Study 1. Avoid using Zykadia in combination with other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible. Monitor heart rate and blood pressure regularly. In cases of symptomatic bradycardia that is not life-threatening, withhold Zykadia until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, evaluate the use of concomitant medications, and adjust the dose of Zykadia. Permanently discontinue Zykadia for life-threatening bradycardia if no contributing concomitant medication is identified; however, if associated with a concomitant medication known to cause bradycardia or hypotension, withhold Zykadia until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, and if the concomitant medication can be adjusted or discontinued, resume Zykadia at a reduced dose as described in Table 1 of the package insert upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring.

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

The most common adverse reactions (incidence of at least 25%) are diarrhea, nausea, vomiting, abdominal pain, fatigue, decreased appetite, and constipation. Key laboratory abnormalities (incidence of at least 25%) were decreased hemoglobin (84%), increased alanine transaminase (80%), increased aspartate transaminase (75%), increased creatinine (58%), increased glucose (49%), decreased phosphate (36%), and increased lipase (28%).

Avoid concurrent use of Zykadia with strong CYP3A inhibitors and strong CYP3A inducers. If concurrent use of a strong CYP3A inhibitor is unavoidable, reduce the dose of Zykadia by approximately one-third. Avoid concurrent use of Zykadia with CYP3A and CYP2C9 substrates with narrow therapeutic indices. Patients should not consume grapefruit and grapefruit juice during treatment with Zykadia. Patients should be instructed to take Zykadia on an empty stomach (i.e., do not take within 2 hours of a meal).

*Xalkori® is a registered trademark of Pfizer Inc.

[1] Morris SW, Kirstein MN, Valentine MB, Dittmer KG, Shapiro DN, Saltman DL, Look AT. "Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma". *Science* 263: 1281–4 (1994).
[2] Soda M, Choi YL, Enomoto M, et al. "Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer". *Nature* 448 (7153): 561–6 (2007).
[3] Galkin AV, Melnick JS, Kim S, Hood TL, Li N, Li L, Xia G, Steensma R, Chopiuk G, Jiang J, Wan Y, Ding P, Liu Y, Sun F, Schultz PG, Gray NS, Warmuth M. "Identification of NVP-TAE684, a potent, selective, and efficacious inhibitor of NPM-ALK". *Proc Natl Acad Sci* U S A.104:270-5 (2007).
[4] Li N, Michellys PY, Kim S, et al. Activity of a potent and selective phase 1 ALK inhibitor LDK378 in naïve and crizotinib-resistant preclinical tumor models. Abstract #B232. 2011 AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics, San Francisco, CA, USA.
[5] Mehra R, et al. Results of a First-in-Human Phase I Study of the ALK Inhibitor LDK378 in Advanced Solid Tumors. Abstract #3007. 2012 American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, USA.
[6] Shaw A, et al. Clinical Activity of the ALK Inhibitor LDK378 in Advanced, ALK-positive NSCLC. Abstract #8010. 2013 American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, USA.
[7] ClinicalTrials.gov. Expanded Treatment Protocol With LDK378 in ALK(+) NSCLC. Available at: http://clinicaltrials.gov/ct2/show/NCT01947608. Accessed March 17, 2014.
[8] Shaw A, et al. Ceritinib in ALK-Rearranged Non–Small-Cell Lung Cancer. *N Engl J Med.* 2014;370(13):1189-97.
[9] Zykadia™ (ceritinib) Prescribing Information. East Hanover, New Jersey, USA: Novartis Pharmaceuticals Corporation; April 2014.