NOVARTIS

מרץ 2016

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

הנדון: Zykadia 150mg
זיקאדיה 150 מ"ג
Hard Gelatin Capsules

התכשיר שבנדון רשום בישראל להתוויה הבאה:

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

המרכיב הפעיל:

Ceritinib 150 mg

העלונים לרופא ולצרכן של התכשירים שבנדון עודכנו.
העדכונים המשמעותיים מפורטים להלן (קו תחתי משמעו תוספת טקסט, ~~קו חוצה~~ משמעו מחיקת טקסט):

בעלון לרופא:

2 DOSAGE AND ADMINISTRATION

2.1 Dosing and Administration

The recommended dose of ZYKADIA is 750 mg orally once daily ~~at the same time each day~~ until disease progression or unacceptable toxicity. Administer ZYKADIA on an empty stomach (i.e., do not administer within 2 hours of a meal) *[see Clinical Pharmacology (12.3)]*.

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If vomiting occurs during the course of treatment, do not administer an additional dose and continue with the next scheduled dose of ZYKADIA.

2.2 Dose Modifications for Adverse Reactions

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Approximately 58% of patients initiating treatment at the recommended dose required at least one dose reduction and the median time to first dose reduction was 7 weeks ~~based on data from 4 clinical studies with ZYKADIA~~.

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Table 1: ZYKADIA Dose Interruption, Reduction, or Discontinuation Recommendations

Criteria	ZYKADIA Dosing
…..	…..
~~Elevated serum lipase~~Lipase or amylase elevation greater than ~~or equal to Grade 3~~2 times ULN	Withhold ~~ZYKADIA~~ and monitor serum lipase ~~or~~and amylase. Resume ZYKADIA with a 150 mg dose reduction ~~if serum lipase or amylase returns~~after recovery to less than ~~or equal to Grade~~ 1.5 times ULN.
~~CTCAE, Common Terminology Criteria for Adverse Events v4.03~~ ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; ILD, interstitial lung disease; ECG, electrocardiogram	

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5 WARNINGS AND PRECAUTIONS

5.1 Severe or Persistent Gastrointestinal Toxicity

Diarrhea, nausea, vomiting, or abdominal pain occurred in 96% of 255 patients including severe cases in 14% of patients treated with ZYKADIA in ~~clinical studies including severe cases in 12% of patients.~~Study 1. Dose modification due to diarrhea, nausea, vomiting, or abdominal pain occurred in 38% of patients.

Monitor and manage patients 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 *[see Dosage and Administration (2.2) and Adverse Reactions (6)]*. ~~If vomiting occurs during the course of treatment, the patient should not take an additional dose, but should continue with the next scheduled dose.~~

5.2 Hepatotoxicity

~~Cases of~~Drug-induced hepatotoxicity occurred in ~~less than 1% of~~ patients treated with ZYKADIA ~~in clinical studies. Increases to grade 3 or 4 ALT elevations were observed in 25% of~~. Elevations in alanine aminotransferase (ALT) greater than 5 times the upper limit of normal (ULN) occurred in 27% of 255 patients ~~receiving ZYKADIA.~~in Study 1. One patient (0.4%) required permanent discontinuation due to elevated transaminases, and jaundice. Concurrent elevations in ALT greater than ~~three~~3 times the ~~upper limit of normal~~ULN and total bilirubin greater than ~~two~~2 times the ~~upper limit of normal~~ULN, with normal alkaline phosphatase, occurred in less than 1% of patients in clinical studies. ~~The majority of cases were manageable with dose interruption and/or dose reduction. Few events required discontinuation of ZYKADIA~~

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5.3 Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, or fatal ILD/pneumonitis ~~occurred~~can occur in patients treated with ZYKADIA ~~in clinical studies.ILD/~~. 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.

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5.4 QT Interval Prolongation

QTc interval prolongation, which may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade de pointes) or sudden death, occurred in patients treated with ZYKADIA in clinical ~~studies. Four~~trials. Three percent (~~4~~3%) of 255 patients experienced a QTc interval increase over baseline greater than 60 msec~~. A central analysis~~ in Study 1. Across the development program of ~~electrocardiogram (ECG) data demonstrated new~~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 ~~in 1 patient (0.2%).~~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 ~~periodic monitoring of~~ electrolytes ~~(e.g., potassium)~~ in patients with congestive heart failure, bradyarrhythmias, ~~or~~electrolyte abnormalities ~~and in patients~~, or those who are taking medications that are known to prolong the QTc interval. ~~In case of vomiting, diarrhea, dehydration, or impaired renal function, correct electrolytes as clinically indicated.~~ 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. 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 *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.2)]*.

5.5 Hyperglycemia

Hyperglycemia ~~occurred~~can occur in patients receiving ZYKADIA ~~in clinical studies.~~. 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.

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5.6 Bradycardia

Bradycardia ~~(including bradycardia and sinus bradycardia)occurred~~can occur in ~~2% of~~ 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 ~~clinical studies~~1% of 255 patients. Bradycardia was reported as an adverse drug reaction in 3% of patients in Study 1.

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~~• Laboratory Tests and Monitoring~~

~~Elevations of lipase and/or amylase occurred in patients receiving ZYKADIA in clinical studies. 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 1 *[see Dosage and Administration (2.2) and Adverse Reactions (6)]*.~~

5.7 Pancreatitis

Pancreatitis, including one fatality, has been reported in less than 1% of patients receiving ZYKADIA in clinical ~~studies~~trials. CTCAE Grade 3-4 elevations of lipase and/or amylase occurred in 15% of patients receiving ZYKADIA in Study 1. 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 1 *[see Dosage and Administration (2.2) and Adverse Reactions (6)]*.

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6 ADVERSE REACTIONS

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

- …..
- ~~Laboratory Tests and Monitoring~~• Pancreatitis *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

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The safety evaluation of ZYKADIA is based on ~~525~~255 ALK-positive patients ~~(515 ALK-positive~~in Study 1 (246 patients with NSCLC ~~and10 ALK-positive~~and
9 patients with other cancers~~)~~ who received ZYKADIA at a dose of 750 mg daily ~~in 4 clinical studies.~~). The median duration of exposure to ZYKADIA was ~~33 weeks~~6 months. The study population characteristics were: median age 53 years, age less than 65 (~~83~~84%), female (~~54~~53%), Caucasian (~~56~~63%), Asian (~~42~~34%), NSCLC adenocarcinoma histology (~~92~~90%), never or former smoker (97%), ECOG PS 0 or 1 (89%), brain metastasis (~~53~~49%), and number of prior therapies 2 or more (~~73%). In a multicenter, single-arm, open-label clinical trial (Study 1), 97% of patients were never or former smokers.~~67%).

Dose ~~adjustment or interruption~~reductions due to adverse reactions occurred in ~~75~~59% of patients treated with ZYKADIA ~~in clinical studies.~~. The most frequent adverse reactions, reported in at least 10% of patients, that led to dose ~~adjustment~~reductions or ~~interruption~~interruptions were: increased ALT (29%), nausea (~~19%),~~ ~~vomiting (19~~20%), increased AST (16%), diarrhea (16%), and ~~increased AST~~vomiting (16%). Serious adverse drug reactions reported in 2%
or more of patients ~~were pneumonia (4%), dyspnea (3%),~~in Study 1 were convulsion ~~(2%),~~ , pneumonia, ILD/pneumonitis ~~(2%), and pyrexia (2%).~~, dyspnea, dehydration, hyperglycemia, and nausea. Fatal adverse reactions in patients treated with ZYKADIA occurred in ~~3~~ 5% of patients, consisting of: pneumonia (4 patients ~~and include interstitial lung disease, multi-organ~~), respiratory failure, ILD/pneumonitis, pneumothorax, gastric hemorrhage, general physical health deterioration, pulmonary tuberculosis, cardiac tamponade, and ~~pneumonia~~sepsis (1 patient each). Discontinuation of therapy due to adverse reactions occurred in ~~9~~10% of patients treated with ZYKADIA. The most frequent adverse drug reactions that led to discontinuation in 1% or more of patients in Study 1 were pneumonia ~~(0.8%),~~ , ILD/pneumonitis ~~(0.8%),~~ and ~~nausea (0.6%).~~decreased appetite.

Tables 2 and 3 summarize the common adverse reactions and laboratory abnormalities observed in ZYKADIA-treated patients ~~at the starting dose of 750 mg in 4 clinical studies~~.

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

	ZYKADIA	
	All Grades	**Grade 3–4**
	%	**%**
Gastrointestinal disorders		
Diarrhea	~~84~~ 86	~~5~~ 6
Nausea	80	~~5~~ 4
Vomiting	~~63~~ 60	~~5~~ 4
Abdominal pain[a]	~~48~~ 54	2
Constipation	~~25~~ 29	0~~.~~ ~~6~~
Esophageal disorder[b]	~~15~~ 16	~~0.~~ ~~4~~ 1

General disorders and administration site		
Fatigue[c]	~~**50**~~ 52	~~**7**~~ 5
Metabolism and nutrition disorders		
Decreased appetite	~~**41**~~ 34	~~**2**~~ 1
Skin and subcutaneous tissue disorders		
Rash[d]	~~**19**~~ 16	0~~.~~ ~~**4**~~
~~**Cardiac**~~**Respiratory, thoracic and mediastinal**		
~~Pericarditis~~[e]Interstitial lung disease/pneumonitis	~~**6**~~ 4	3

*National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03)
[a]Abdominal pain (abdominal pain, upper abdominal pain, abdominal discomfort, epigastric discomfort)
[b]Esophageal disorder (dyspepsia, gastroesophageal reflux disease, dysphagia)
[c]Fatigue (fatigue, asthenia)
[d]Rash (rash, maculopapular rash, acneiform dermatitis)
[e]~~Pericarditis (pericarditis, pericardial effusion)~~

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ZYKADIA included neuropathy (~~16~~17%; comprised of paresthesia, muscular weakness, ~~hypoesthesia, peripheral neuropathy,~~ gait disturbance, peripheral neuropathy, hypoesthesia, peripheral sensory neuropathy, dysesthesia, ~~hypotonia,~~ neuralgia, ~~formication, neurotoxicity,~~ peripheral motor neuropathy, ~~peroneal nerve palsy~~hypotonia, or polyneuropathy), vision disorder (~~8%;~~9%; comprised of vision impairment, blurred vision, ~~diplopia,~~ photopsia, ~~reduced visual acuity,~~ accommodation disorder, presbyopia, or reduced visual ~~field defect), ECG QT~~acuity), prolonged ~~(6%), pneumonitis (3%, pneumonitis or ILD),~~ QT interval (4%), and bradycardia (~~2%; bradycardia or sinus bradycardia) , renal failure (2%; renal failure or acute renal failure), renal impairment (1%; renal impairment or azotemia), hepatotoxicity (0.6%; hepatotoxicity, drug-induced liver injury, cholestatic hepatitis, or hepatocellular injury), and pancreatitis (0.4~~3%).

Table 3: Key Laboratory Abnormalities Occurring in >10% (All NCI CTCAE Grades) of ALK-Positive Patients Treated with ZYKADIA in Study 1

	ZYKADIA	
	All Grades	**Grade 3–4**
	%	**%**
Hemoglobin decreased	84	5
Alanine transaminase (ALT) increased	~~**74**~~ 80	~~**25**~~ 27
Aspartate transaminase (AST) increased	~~**71**~~ 75	~~**12**~~ 13
Creatinine increased	~~**61**~~ 58	2
Glucose increased	~~**50**~~ 49	~~**12**~~ 13
~~Hemoglobin decreased~~	~~**42**~~	~~**5**~~
Phosphate decreased	36	~~**6**~~ 7
~~Lipase increased~~[a]	~~**30**~~	~~**11**~~
~~Amylase~~Lipase increased	~~**25**~~ 28	~~**5**~~1 0
Bilirubin (total) increased	~~**10**~~ 15	~~**0.6**~~ 1

[a]~~Based on a multicenter, single-arm, open-label clinical trial (Study 1)~~

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

(http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il).

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8.5 Geriatric Use

Clinical studies of ZYKADIA did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. Of the ~~525~~255 patients in ~~4 studies~~Study 1 who received ZYKADIA at the recommended dose, ~~89 (17~~40 (16%) were 65 years or older.

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11 DESCRIPTION

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ZYKADIA is supplied as printed hard-gelatin capsules containing 150 mg of ceritinib and the following inactive ingredients: ~~**Colloidal Silicon Dioxide, Low-Substituted**~~ microcrystalline cellulose, low-substituted hydroxypropyl cellulose, sodium starch glycolate, magnesium stearate, colloidal silicon dioxide, ~~hydroxypropylcellulose~~, ~~magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and~~ hard gelatin capsule shells and black printing ink.
~~-~~The capsule shell is composed of gelatin, titanium dioxide (E171), and indiogotine – FD&C Blue 2 (E132)~~,~~.
The black printing ink is composed of Shellac glaze 45%, Iron oxide black (E172), Propylene glycol and Ammonium hydroxide 28%.~~-~~ ~~titanium dioxide and printing ink, black~~.

The product contains 1.54 mg sodium per dose.

12 CLINICAL PHARMACOLOGY

~~**Pharmacotherapeutic group, ATC: L01XE28**~~

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12.2 Pharmacodynamics

Cardiac Electrophysiology

~~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 greater than 500 msec~~ in ~~1 patient (0.2%). There were 23~~an open-label, dose-escalation, and expansion study. A total of 304 patients ~~(4%)~~were treated with ZYKADIA doses ranging from 50 to 750 mg with 255 patients treated with ZYKADIA 750 mg. One of 304 patients (less than 1%) was found to have a QTc greater than 500 msec and 10 patients (3%) had an increase from baseline QTc greater than 60 msec. ~~A concentration-~~A central tendency analysis of the QTc ~~response analysis based on data from a global phase I study demonstrated that~~ data at average steady-state concentrations demonstrated that the upper bound of the 2-sided 90% CI for QTc was 16 msec at ZYKADIA 750 mg. A pharmacokinetic/pharmacodynamic analysis suggested concentration-dependent QTc interval prolongation *[see Warnings and Precautions (5.4)]*.

Based on central review of ECG data ~~in 4 clinical studies with ZYKADIA, 20~~, 2 of ~~519 evaluable~~304 patients (~~4~~0.7%) had bradycardia defined as less than 50 beats per minute ~~with a 25% decrease from baseline.~~ Bradycardia ~~(including bradycardia and sinus bradycardia)~~was reported as an adverse drug reaction in ~~2~~3% of patients in Study 1.

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17 PATIENT COUNSELING INFORMATION

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- Inform patients of the signs and symptoms of pancreatitis and the need to monitor lipase and amylase levels prior to the start of treatment and periodically thereafter as clinically indicated *[see Warnings and Precautions (5.7)]*.

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בעלון לצרכן:

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בעיות ריאות (דלקת ריאות - פנאומוניטיס). זיקאדיה עלולה לגרום לבצקת (דלקת) חמורה או מסכנת חיים של הריאות במהלך הטיפול שעלולה להביא למוות. התסמינים יכולים להיות דומים לתסמינים של מחלת סרטן הריאות. יידע את הרופא המטפל שלך מיד אם יש לך תסמינים חדשים או אם תסמינים כלשהם מחמירים, כולל:

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3. כיצד תשתמש בתרופה?

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יש לקחת זיקאדיה פעם ביום באותה שעה.

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4. תופעות לוואי

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לאנשים עם סוכרת או אי סבילות לגלוקוז או כאלה שלוקחים תרופה ממשפחת הקורטיקוסטרואידים יש סיכון מוגבר לרמה גבוהה של סוכר בדם בזמן הטיפול בזיקאדיה. עקוב אחר ההוראות של הרופא המטפל שלך לגבי ניטור בדוק את רמת הסוכר בדם שלך לפני תחילת הטיפול בזיקאדיה ולפי הצורך במהלך הטיפול בזיקאדיה. התקשר לרופא שלך מיד אם יש לך תסמינים של רמה גבוהה של סוכר בדם, כולל:

.....

- **דלקת בלבלב (פנקריאטיטיס)**
- זיקאדיה יכולה לגרום לפנקריאטיטיס שהובילה למוות. אתה עשוי לפתח עליה ברמות של אנזימי לבלב בדם, שעשויה להיות סימן לפנקריאטיטיס. הסימנים והסימפטומים של פנקריאטיטיס כוללים כאב בבטן העליונה שעשוי להתפשט לגב ולהחמיר עם אכילה. על הרופא המטפל שלך לבצע בדיקות דם על מנת לבדוק את רמות אנזימי הלבלב בדם שלך לפני שאתה מתחיל טיפול בזיקאדיה ולפי הצורך במהלך הטיפול שלך.

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ניתן לדווח על תופעות לוואי למשרד הבריאות באמצעות לחיצה על הקישור "דיווח על תופעות לוואי עקב טיפול תרופתי" שנמצא בדף הבית של אתר משרד הבריאות (www.health.gov.il) המפנה לטופס המקוון לדיווח על תופעות לוואי,

או ע"י כניסה לקישור :
https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

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6. מידע נוסף

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כל כמוסה מכילה 1.54 מ״ג נתרן.

בנוסף, חלו בעלונים עדכונים עריכתיים.

העלונים לרופא ולצרכן נשלח למאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על-ידי פניה לבעל הרישום.

בברכה,
אסנת מירון - עוזרי
רוקחת ממונה

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