נובמבר 2021

Alecensa®

אלצנזה

Alectinib 150 mg

Capsules

רופא/ה יקר/ה, רוקח/ת יקר/ה,

חברת רוש פרמצבטיקה (ישראל) בע"מ מבקשת להודיעכם על מספר עדכונים שבוצעו בעלון לרופא ובעלון לצרכן של התכשיר Alecensa.

בהודעה זו מצוינים רק עדכונים מהותיים ועדכונים אשר מהווים החמרה.

ההתוויות הרשומות לתכשיר בישראל:

- Alectinib is indicated for the treatment of patients with ALK positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who progressed on or are intolerant to crizotinib.
- Alecensa as monotherapy is indicated for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

הסבר:

טקסט עם קו תחתי מציין טקסט שהוסף לעלון.
טקסט עם קו תחתי הצבוע בצהוב מציין החמרה.
~~טקסט עם קו חוצה~~ מציין טקסט שהוסר מן העלון.

למידע נוסף יש לעיין בעלון לרופא ובעלון לצרכן כפי שנשלחו למשרד הבריאות.

העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על-ידי פנייה לבעל הרישום: רוש פרמצבטיקה (ישראל) בע"מ, ת.ד 6391 , הוד השרון 4524079 טלפון 09-9737777. כתובתנו באינטרנט: www.roche.co.il.

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מיכל קליין
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עדכונים מהותיים בעלון לרופא

בסעיף 4.8 Undesirable effects עודכן המידע הבא:

Summary of the safety profile

The data described below reflect exposure to Alecensa in 405 patients with ALK-positive advanced NSCLC who participated in one randomised Phase III clinical trial (BO28984) and in two single-arm phase II clinical trials (NP28761, NP28673). These patients were treated with the recommended dose of 600 mg twice daily. In the phase II clinical trials (NP28761, NP28673; N=253), the median duration of exposure to Alecensa was 11.2 months. In BO28984 (ALEX; N=152) the median duration of exposure to Alecensa was ~~17.9~~ 28.1 months, whereas the median duration of exposure to crizotinib was 10.~~7~~ 8 months.

The most common adverse drug reactions (ADRs) (≥ 20%) were constipation ~~(35%),~~ myalgia, oedema ~~(30%, including oedema peripheral, oedema, generalised oedema, eyelid oedema, periorbital oedema, face oedema~~, anaemia, rash, increased bilirubin and ~~localised oedema), and myalgia (28%, including myalgia and musculoskeletal pain).~~ nausea.

Tabulated list of adverse drug reactions

Table 3 lists the ADRs occurring in patients who received Alecensa across two phase II clinical trials (NP28761, NP28673) and one phase III clinical trial (BO28984; ALEX), and during post-marketing.

The ADRs listed in Table 3 are presented by system organ class and frequency categories, defined using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000). Within each system organ class, undesirable effects are presented in order of decreasing frequency.

Table 3 ADRs reported in Alecensa clinical trials (NP28761, NP28673, BO28984; N=405) and during post-marketing

System organ class ADRs (MedDRA)		**Alecensa N=405**		
	~~**All grades (%)**~~	**Frequency category (all grades)**	~~**Grades**~~**Frequency category (grades 3-4 ~~(%)~~)**	
Blood and lymphatic system disorders				
Anaemia[1]	~~17~~	Very common	Common~~3.0~~	
Haemolytic anaemia[2]		Uncommon	-~~*~~	
Nervous system disorders				
~~Dysgeusia~~~~**~~~~Dysgeusia[3]	~~5.2~~	Common	~~0.2~~ Uncommon	
Eye disorders				
Vision ~~disorders~~~~*~~~~disorders[4]		~~8.6~~Very common	~~*~~ ~~Common~~	~~0~~
Cardiac disorders				
~~Bradycardia~~~~*~~~~Bradycardia[5]		~~8.9~~Very common	-~~*~~ ~~Common~~	~~0~~
Respiratory, thoracic and mediastinal disorders				
Interstitial lung disease / pneumonitis		Common~~0.7~~	Uncommon	~~0.2~~
Gastrointestinal disorders				
Constipation	~~35~~	Very common	~~0~~Uncommon	
Nausea	~~19~~	Very common	~~0.5~~Uncommon	
Diarrhoea	~~16~~	Very common	~~0.7~~Common	
Vomiting	~~11~~	Very common	~~0.2~~Uncommon	
~~Stomatitis~~~~*~~~~Stomatitis[6]	~~3.0~~	Common	~~0~~ -~~*~~	
Hepatobiliary disorders				
Increased ~~bilirubin~~~~*~~~~bilirubin[7]	~~18~~	Very common	~~3.2~~Common	
Increased AST	~~15~~	Very common	~~3.7~~Common	
Increased ALT	~~14~~	Very common	~~3.7~~Common	
Increased alkaline ~~phosphatase~~~~**~~~~phosphatase[8]	~~6.2~~	Common	~~0.2~~Uncommon	
Drug-induced liver ~~injury~~~~*~~~~injury[9]		~~0.7~~Uncommon	Uncommon	~~0.7~~
Skin and subcutaneous tissue disorders				
~~Rash~~~~*~~~~Rash[10]	~~18~~	Very common	~~0.5~~Common	
Photosensitivity	~~9.1~~	Common	~~0.2~~Uncommon	
Musculoskeletal and connective tissues disorders				
~~Myalgia~~~~*~~~~Myalgia[11]	~~28~~	Very common	~~0.7~~Common	
Increased blood creatine phosphokinase	~~10~~	Very common	~~3.2~~Common	
Renal and urinary disorders				
Blood creatinine increased	~~7.2~~	Common	~~0.7*~~Uncommon~~**~~	
Acute kidney injury		~~1.0~~Common	Common~~**~~	~~1.0*~~
General disorders and administration site conditions				
~~Oedema~~~~**~~~~Oedema[12]	~~30~~	Very common	~~0.7~~Common	

System organ class ADRs (MedDRA)		Alecensa N=405	
	~~All grades (%)~~	Frequency category (all grades)	~~Grades~~Frequency category (grades 3-4 ~~(%)~~)
Investigations			
Weight increased	~~12~~	Very common	~~0.7~~Uncommon

* No grade 3-4 ADRs were observed

** Includes one Grade- 5 event

~~** Increased alkaline phosphatase was reported in the post-marketing period and in pivotal phase II and phase III clinical trials.~~

[1)] includes cases of anaemia and haemoglobin decreased

~~[2)] includes cases of dysgeusia and hypogeusia~~

[2)] Cases of haemolytic anaemia have been reported in the post-marketing period and two cases suggestive of haemolytic anaemia have been reported in clinical trials. The following studies (N=716) have been included in the frequency calculation: NP28761, NP28673, BO28984, MO29750, BO39694, BO29554 cohort A, YO29449.

[3)] includes cases of dysgeusia, hypogeusia, and taste disorder

[4)] includes cases of blurred vision, visual impairment, vitreous floaters, reduced visual acuity, asthenopia, ~~and~~ diplopia, photophobia and photopsia

[5)] includes cases of bradycardia and sinus bradycardia

[6)] includes cases of stomatitis and mouth ulceration

[7)] includes cases of blood bilirubin increased, hyperbilirubinaemia ~~and~~, bilirubin conjugated increased~~-~~, and blood bilirubin unconjugated increased

[8)] Increased alkaline phosphatase was reported in the post-marketing period and in pivotal phase II and phase III clinical trials

[9)] includes two patients with reported MedDRA term of drug-induced liver injury as well as one patient with reported Grade 4 increased AST and ALT who had documented drug-induced liver injury by liver biopsy

~~8~~[10)] includes cases of rash, rash maculopapular, dermatitis acneiform, erythema, rash generalised, rash papular, rash pruritic, rash macular and exfoliative rash

~~9~~[11)] includes cases of myalgia ~~and~~, musculoskeletal pain, and arthralgia

~~10~~[12)] includes cases of oedema peripheral, oedema, generalised oedema, eyelid oedema, periorbital oedema, face oedema and localised oedema

[…]

Hepatotoxicity

Across clinical trials (NP28761, NP28673, BO28984) two patients with Grade 3-4 AST/ALT elevations had documented drug induced liver injury by liver biopsy.

In addition, one patient experienced a Grade 4 adverse event of drug-induced liver injury.

Two of these cases led to withdrawal from Alecensa treatment. Adverse reactions of increased AST and ALT levels (~~15~~17% and ~~14~~16% respectively) were reported in patients treated with Alecensa across clinical trials (NP28761, NP28673, BO28984). The majority of these events were of Grade 1 and 2 intensity, and events of Grade ≥ 3 were reported in 3.7% and 3.7% of the patients for increased AST and ALT levels, respectively. The events generally occurred during the first 3 months of treatment, were usually transient and resolved upon temporary interruption of Alecensa treatment (reported for 1.5% and 3.0% of the patients, respectively) or dose reduction (2.~~2~~0% and 1.~~2~~5%,

respectively). In 1.2% and 1.5% of the patients, AST and ALT elevations, respectively, led to withdrawal from Alecensa treatment.

Grade 3 or 4 ALT or AST elevations were each observed in 5% of patients receiving Alecensa versus ~~15~~16% and 11% of patients receiving crizotinib in the phase III clinical trial BO28984.

Adverse reactions of bilirubin elevations were reported in ~~18~~ 21% of the patients treated with Alecensa across clinical trials (NP28761, NP28673, BO28984). The majority of the events were of Grade 1 and 2 intensity; Grade 3 events were reported in 3.~~2~~ 7% of the patients. The events generally occurred during the first 3 months of treatment, were usually transient and the majority resolved upon dose modification.

In ~~5.2~~ 7.7% of patients, bilirubin elevations led to dose modifications and in ~~1.5~~ 2.0% of patients, bilirubin elevations led to withdrawal from Alecensa treatment.
In the phase III clinical trial BO28984, Grade 3 or 4 bilirubin elevations occurred in 3.~~3~~9% of patients receiving Alecensa versus no patient receiving crizotinib.

Concurrent elevations in ALT or AST greater than or equal to three times the ULN and total bilirubin greater than or equal to two times the ULN, with normal alkaline phosphatase, occurred in one patient (0.2%) treated in Alecensa clinical trials.

Patients should be monitored for liver function including ALT, AST, and total bilirubin as outlined in section 4.4 and managed as recommended in section 4.2.

Bradycardia
Cases of bradycardia (~~8.9~~ 11%) of Grade 1 or 2 have been reported in patients treated with Alecensa across clinical trials (NP28761, NP28673, BO28984). No patients had events of Grade≥3 severity. There were 66 of 365- patients (18%) treated with Alecensa who had post-dose heart rate values below 50 beats per minutes (bpm).
In the phase III clinical trial BO28984 15% of patients treated with Alecensa had post-dose heart rate values below 50 bpm versus ~~20~~ 21% of patients treated with crizotinib.
Patients who develop symptomatic bradycardia should be managed as recommended in sections 4.2 and 4.4. No case of bradycardia led to withdrawal from Alecensa treatment.

Severe myalgia and CPK elevations
Cases of myalgia (~~28~~35%) including myalgia events (~~22%) and~~23%), musculoskeletal pain (~~7.4~~0.5%), and arthralgia (19%) have been reported in patients treated with Alecensa across clinical trials (NP28761, NP28673, BO28984). The majority of events were Grades 1 or 2 and ~~three~~four patients (1.0~~.7~~%) had a Grade 3 event. Dose modifications of Alecensa treatment due to these adverse events were only required for two patients (0.5%); Alecensa treatment was not withdrawn due to these events of myalgia. Elevations of CPK occurred in ~~43~~48% of ~~362~~ 363 patients with CPK laboratory data available across clinical trials (NP28761, NP28673, BO28984) with Alecensa. The incidence of Grade ≥ 3 elevations of CPK was ~~3.7~~ 4.2%. Median time to Grade ≥ 3 CPK elevation was 14 days across trials (NP28761, NP28673, BO28984). Dose modifications for elevation of CPK occurred in 3.~~2~~5% of patients; withdrawal from Alecensa treatment did not occur due to CPK elevations. In the clinical trial BO28984, severe arthralgia was reported in one patient (0.7%) in the alectinib arm and in two patients (1.3%) in the crizotinib arm. Grade > 3 elevation of CPK was reported for 3.9% of patients receiving Alecensa and 3.3% of patients receiving crizotinib.

~~Severe myalgia has not been reported in the clinical trial BO28984. Grade 3 elevation of CPK was reported for 2.6% of patients receiving Alecensa and 1.3% of patients receiving crizotinib; and median time to Grade 3 CPK elevation was 27.5 days and 369 days, respectively, in the pivotal phase III clinical trial BO28984 (ALEX).~~

Gastrointestinal effects
Constipation (~~35~~38%), nausea (~~19~~20%), diarrhoea (~~16~~19%) and vomiting (~~11~~14%) were the most commonly reported gastrointestinal (GI) reactions. Most of these events were of mild or moderate

severity; Grade 3 events were reported for diarrhea (1.0~~.7~~%), nausea (0.5%), ~~and~~ vomiting (0.2%), and constipation (0.2%). These events did not lead to withdrawal from Alecensa treatment. Median time to onset for constipation, nausea, diarrhea, and/or vomiting events across clinical trials (NP28761, NP28673, BO28984) was ~~21~~22 days. The events declined in frequency after the first month of treatment.

In the phase III clinical trial BO28984, Grade 3 and 4 events of nausea, diarrhoea and constipation were reported in one patient each (0.~~2%) experienced a Grade 4 event of nausea~~ 7%) in the ~~Alecensa~~ alectinib arm and the incidence of Grade 3 and 4 events ~~for~~ of nausea, diarrhoea and vomiting~~, and diarrhoea~~ was 3.3%, ~~3.3%, and~~ 2.0% and 3.3%, respectively, in the crizotinib arm.

בסעיף 6.4 Special precautions for storage עודכן המידע הבא:

Do not store above 30°C.
~~For the bottle package: Shelf life after first opening: 12 months.~~
Store in the original package to protect from light and keep the bottle tightly closed in order to protect from moisture.

עדכונים מהותיים בעלון לצרכן

בסעיף 2. לפני השימוש בתרופה עודכן המידע הבא:

[...]

אלצנזה עם מזון ושתייה
יש ליטול את התרופה עם מזון.
יש להיזהר בשתיית מיץ אשכוליות, אכילת אשכוליות או חושחש/תפוז מר בזמן הטיפול באלצנזה הואיל והם עלולים לשנות את כמות התרופה בגופך.

בסעיף 4. תופעות לוואי עודכן המידע הבא:

[...]

תופעות לוואי שכיחות מאוד (עלולות להשפיע על יותר ממשתמש אחד מתוך עשרה):
- תוצאות חריגות בבדיקות הדם שנועדו לאתר האם יש בעיות בכבד (רמות גבוהות של של אלנין אמינוטראנספראז ~~טראנסאמינאז~~, אספארטאט אמינוטראנספראז ובילירובין)
- תוצאות חריגות בבדיקות הדם שנועדו לאתר האם יש נזק לשריר (רמות גבוהות של קראטין פוספוקינאז)
- אתה עלול להרגיש עייף, חלש או קצר נשימה עקב ירידה במספר תאי הדם האדומים – אנמיה.
- הקאה – במידה והקאת לאחר נטילת מנה של אלצנזה, אל תיקח מנה נוספת, עליך לקחת את המנה הבאה בזמן הרגיל
- עצירות
- שלשול
- בחילה
- ראייה מטושטשת, אובדן ראייה, ראיית נקודות שחורות או כתמים לבנים, ראייה כפולה (בעיות בעיניים)
- פריחה
- נפיחות אשר נגרמת עקב הצטברות נוזלים בגוף (בצקת)
- עליה במשקל

תופעות לוואי שכיחות (עלולות להשפיע על עד משתמש אחד מתוך עשרה):
- תוצאות חריגות של בדיקות דם לבדיקת תפקוד כליות (רמה גבוהה של קריאטינין).
- ~~ראייה מטושטשת, אובדן ראייה, ראיית נקודות שחורות או כתמים לבנים, ראייה כפולה (בעיות בעיניים)~~
- תוצאות חריגות של בדיקות דם לבדיקת מחלת כבד או בעיות בעצמות (רמות גבוהות של אלקאלין פוספאטאז)
- דלקת ברירית הפה
- רגישות לשמש- אין להיחשף לשמש לזמן ממושך בזמן נטילת אלצנזה ולמשך 7 ימים לאחר הפסקת הטיפול.
- עליך לשים קרם הגנה ושפתון עם מקדם הגנה של SPF 50 ומעלה כדי למנוע כוויות שמש.
- שינוי בחוש הטעם

• פגיעה מהירה בפעילות הכליה (בעיות כליה)

תופעות לוואי שאינן שכיחות (עלולות להשפיע על עד משתמש אחד מתוך מאה):
• אתה עלול להרגיש עייף, חלש או קצר נשימה כתוצאה מהרס לא תקין של תאי דם אדומים (אנמיה המוליטית)