דצמבר 2024

LUMYKRAS (Sotorasib 120 mg)
Film-Coated Tablets

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

אמג'ן אירופה בי וי, בעלת הרישום, מבקשת להודיעך על עדכונים בעלונים לרופא ולצרכן של התכשיר **LUMYKRAS**. בהודעה זו מפורטים השינויים המשמעותיים וההחמרות בלבד. קו תחתי מציין תוספת טקסט, קו חוצה מציין מחיקה.

ההתוויות הרשומות לתכשיר:

LUMYKRAS is indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an approved test, who have received at least one prior systemic therapy.

שינויים בעלון לרופא:

4.4 Special warnings and precautions for use

Hepatotoxicity

Sotorasib can cause hepatotoxicity, which may lead to drug-induced liver injury (DILI) and hepatitis. Sotorasib has been associated with transient elevations of serum transaminases (ALT and AST), alkaline phosphatase and total bilirubin in 960 mg monotherapy clinical trials. In a total of 740 patients with *KRAS G12C*-mutated solid tumours who received LUMYKRAS 960 mg monotherapy daily, the incidence for hepatotoxicity is highest in the sub-group of patients with recent (≤ 3 months) immunotherapy (38%) prior to starting LUMYKRAS, as compared to those who started LUMYKRAS either more than 3 months after last dose of immunotherapy (17%) or those who never received immunotherapy (22%). Regardless of time from prior immunotherapy, 87% of~~. These~~ elevations improved or resolved with ~~dose modification or permanent~~ interruption of LUMYKRAS treatment and treatment with corticosteroids. Elevated liver enzymes led to discontinuation of treatment in 10%, 2% and 0% of patients with prior immunotherapy within ≤ 3 months, with prior immunotherapy within > 3 months and no prior immunotherapy, respectively. Among 740 patients with *KRAS G12C*-mutated solid tumours who received 960 mg orally once daily, 26% ~~and did not result in any cases of liver failure or fatal cases in clinical studies. Among patients who~~ experienced hepatotoxicity~~, 38~~and 13% had hepatotoxicity leading to dose interruption and/or dose reduction. Overall, ~~26~~41% of patients with hepatotoxicity received concurrent corticosteroids. Cases of liver enzyme increase can be asymptomatic. Patients should be monitored for liver function (ALT, AST, alkaline phosphatase and total bilirubin) prior to the start of LUMYKRAS, every 3 weeks for the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients ~~who develop transaminase and/or bilirubin elevations~~ with recent immunotherapy and in patients with serious hepatotoxicity events. Based on the severity of the laboratory abnormalities, treatment with LUMYKRAS must be ~~stopped~~interrupted until recovered to ≤ ~~grade 1~~3 × ULN or to ≤ 3 baseline ~~grade~~(if baseline abnormal) and treatment with corticosteroids considered, and the dose of LUMYKRAS must be either ~~be~~ modified or permanently discontinued ~~treatment as recommended~~ (see section 4.2).

Interstitial Lung Disease (ILD)/pneumonitis

LUMYKRAS can cause ILD/pneumonitis that can be fatal. ILD/pneumonitis occurred in patients treated with LUMYKRAS with prior exposure to immunotherapy or radiotherapy (see section 4.8). Recent (≤ 3 months) immunotherapy prior to starting LUMYKRAS may be considered a risk factor for ILD/pneumonitis. Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g. dyspnea, cough, fever). Immediately withhold LUMYKRAS in patients with suspected ILD/pneumonitis and permanently discontinue LUMYKRAS if no other ~~potential~~ causes of ILD/pneumonitis are identified (see section 4.2).

Use in population with hepatic impairment

There are no data on the clinical safety and efficacy of multiple doses of LUMYKRAS when administered to patients with moderate and severe hepatic impairment (Child-Pugh B and C). No dose recommendation can be made.

4.5 Interaction with other medicinal products and other forms of interaction

Avoid co-administration of LUMYKRAS with CYP3A4 substrates with narrow therapeutic indices, including but not limited to alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, hormonal contraceptives, pimozide, quinidine, sirolimus, ~~and~~ tacrolimus, amlodipine and manidipine. If co-administration cannot be avoided, adjust the CYP3A4 substrate dose in accordance with the current summary of product characteristics.

4.8 Undesirable effects

Summary of the safety profile

Adverse drug reactions (ADRs) described in table 3 reflect exposure to sotorasib 960 mg once daily as monotherapy in 740 patients with *KRAS G12C*-mutated solid tumours across multiple clinical studies, including CodeBreaK 200, CodeBreaK 100 phase 2 part A, and CodeBreaK 100 phase 2 part B (dose comparison sub-study) and three phase 1 studies.

The most common adverse reactions in patients treated with LUMYKRAS 960 mg once daily were diarrhea (36.6~~4~~%), nausea (24.7~~5~~%), ~~and~~ fatigue (~~21~~19.1%), vomiting (16.1%), arthralgia (15.3%), and decreased appetite (15.1%). The most common severe (grade ≥ 3) adverse reactions were diarrhea (6.9%), increased ALT (5.9%)~~,~~ and increased AST (4.6~~%), and diarrhea (4~~%). The most common adverse reactions leading to permanent discontinuation of treatment were increased ALT (1.5%) and increased AST (1.1%) and DILI (1%). The most common adverse reactions leading to dose modification were diarrhea (11.4%), increased ALT (5.9~~6%), diarrhea (6~~%), increased AST (~~6~~5.7%), nausea (3.8%), increased blood alkaline phosphatase (~~3~~2.4%) and vomiting (2%).

Table 3. Adverse reactions

MedDRA system organ class	**Very common** **(≥ 1/10)**	**Common** **(≥ 1/100 to < 1/10)**	**Uncommon** **(≥ 1/1,000 to < 1/100)**
Nervous system disorders	~~Headache~~	Headache	
Respiratory, thoracic and mediastinal disorders	Cough Dyspnea	ILD/pneumonitis	~~ILD/pneumonitis~~
Hepatobiliary disorders		Drug-induced liver injury	Hepatitis
Renal and urinary disorders			Renal impairment Renal failure Chronic kidney disease Acute kidney injury
General disorders and administration site conditions	Fatigue ~~Pyrexia~~	Pyrexia	
Metabolism and nutrition disorders	Decreased appetite	Hypokalaemia	

[a] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower

Description of selected adverse reactions

Elevated liver enzymes

In clinical studies, transient elevations of serum transaminases were observed (see section 4.4). ~~E~~Among 740 patients who received LUMYKRAS 960 mg once daily as monotherapy, elevations of ALT occurred in 12.8~~14~~% of patients~~subjects~~ and elevations of AST in 13.1~~16~~% of patients~~subjects~~, with a median time to onset of 6~~8~~ weeks (range: 1 to 103~~42~~) and 6~~8~~ weeks (range: 0 to 42), respectively. Elevations of ALT resulted in dose interruption and/or reduction in ~~6~~5.9~~.1~~% of patients~~subjects~~, and elevations of AST resulted in dose interruption and/or reduction in 5.7~~6.1~~% of patients. Elevated bilirubin occurred in 3.2% of patients and resulted in dose interruption and/or reduction in 0.9% of patients~~subjects~~.

ILD/pneumonitis

In clinical studies, among 740~~359~~ patients who received LUMYKRAS 960 mg once daily as monotherapy, ILD/pneumonitis occurred in 1.9~~0.8~~% of patients; ILD/pneumonitis was~~all cases were~~ grade 3 or 4 at onset~~.~~ on 0.8% of patients. A case of fatal ILD occurred in a patient with metastatic NSCLC stage IVB treated with LUMYKRAS in a clinical trial. The patient developed lower respiratory

tract infection with a fatal outcome despite steroids and antibiotics treatment. The fatal ILD occurred in a setting of massive disease progression. The median time to first onset for ILD/pneumonitis was 10.62 weeks (range: 2 to 43.318 weeks). LUMYKRAS was discontinued due to ILD/pneumonitis in 0.96% of patients (see sections 4.2 and 4.4).

שינויים בעלון לצרכן:

2. לפני שימוש בתרופה

תרופות אחרות ולומיקראס

לומיקראס עלולה להפחית את יעילותן של התרופות הבאות:

- תרופות המשמשות לטיפול בכאבים עזים, כגון אלפנטניל או פנטניל;
- תרופות המשמשות בהשתלת איברים למניעת דחיית איברים, כגון ציקלוספורין, סירולימוס, אוורולימוס או טקרולימוס;
- תרופות המשמשות להפחתת לחץ-דם גבוה, כדוגמת: אמלודיפין ומנידיפין.

4. תופעות לוואי

שכיחות מאוד (עלולות להשפיע על יותר מ-1 מתוך 10 מטופלים)

- ~~חום;~~
- ~~כאב ראש~~ירידה בתאבון.

שכיחות (עלולות להשפיע על עד 1 מתוך 10 מטופלים)

- כאב ראש;
- חום;
- דלקת ריאות הנקראת "מחלת ריאות אינטרסטיציאלית" (interstitial lung disease);
- שינויים בבדיקות דם (ירידה ברמות אשלגן בדם).

שאינן שכיחות (עלולות להשפיע על עד 1 מתוך 100 מטופלים)

- בעיות בכליות, כולל כשל כלייתי;
- ~~דלקת ריאות הנקראת "מחלת ריאות אינטרסטיציאלית"~~דלקת כבד (הפטיטיס).

העלון לרופא נשלח לפרסום במאגר התרופות של אתר משרד הבריאות, וניתן לקבלו גם על-ידי פניה למפיץ המקומי של התרופה, חברת מדיסון פארמה.
שרות לקוחות: Medison-CS@medison.co.il טלפון: 5634*

בברכה,
אמג'ן אירופה בי וי