

רופא/ה נכבד/ה
רוקח/ת נכבד/ה,

חברת אלי לילי ישראל בע"מ מבקשת להודיעכם כי עודכנו העלונים לרופא ולצרכן של התכשירים:

RETEVMO 40 mg tablets, RETEVMO 80 mg tablets, RETEVMO 120 mg tablets, RETEVMO 160 mg tablets

בהודעה זו נכללים השינויים המהותיים בלבד. שינויים המהווים החמרה מסומנים בצהוב, מידע שהתווסף מסומן בכחול ומידע שהוסר מסומן באדום. ישנם עדכונים נוספים.

העלונים המעודכנים לרופא ולצרכן מפורסמים במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפסים על ידי פנייה לבעל הרישום:

אלי לילי ישראל בע"מ, רח' השיזף 4, רעננה, טל': 09-9606234

בברכה,
ליאת אטיאס
רוקחת ממונה

RETEVMO 40 MG TABLETS RETEVMO 80 MG TABLETS RETEVMO 120 MG TABLETS RETEVMO 160 MG TABLETS	שם התכשיר
SELPERCATINIB	החומר הפעיל
TABLETS	צורת מינון
<ul style="list-style-type: none"> •Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer RETEVMO is indicated for the treatment of adult patients with metastatic RET fusion-positive non-small cell lung cancer (NSCLC). •RET-Mutant Medullary Thyroid Cancer RETEVMO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy. •RET Fusion-Positive Thyroid Cancer RETEVMO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). •Other RET Fusion-Positive Solid Tumors RETEVMO as monotherapy is indicated for the treatment of adults with advanced RET fusion-positive solid tumors, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted. 	ההתוויה המאושרת לתכשיר

העדכונים העיקריים בעלון לרופא הינם:

5 WARNINGS AND PRECAUTIONS

[...]

5.6 Hypersensitivity

Hypersensitivity RETEVMO can cause hypersensitivity, including severe skin reactions such as Stevens Johnson Syndrome. All grade hypersensitivity occurred in 6% of patients receiving RETEVMO, including Grade 3 Hypersensitivity in 1.9%. The median time to onset was 1.9 weeks (range: 5 days to 2 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminitis. **Stevens Johnsons Syndrome has been observed in the post-**

marketing setting [see Adverse Reactions (6.2)]. Discontinue RETEVMO in patients with Stevens Johnson Syndrome.

If hypersensitivity occurs, withhold RETEVMO and begin corticosteroids at a dose of 1 mg/kg prednisone (or equivalent). Upon resolution of the event, resume RETEVMO at a reduced dose and increase the dose of RETEVMO by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity [see Dosage and Administration (2.5)]. Continue steroids until patient reaches target dose and then taper. Permanently discontinue RETEVMO for recurrent hypersensitivity.

7 ADVERSE REACTIONS

[...]

7.1 Clinical Trials Experience

[...]

LIBRETTO-121

The safety population described below reflects exposure to RETEVMO as a single agent at 92 mg/m² orally twice daily evaluated in 2736 patients with advanced solid tumors harboring an activating RET alteration in LIBRETTO-121 [see Clinical Studies (13)]. Among the 2736 pediatric and adolescent patients who received RETEVMO, 8486% were exposed for 6 months or longer and 5972% were exposed for greater than one year.

The median age was 13 years (range: 2 to 20 years); 2231% were pediatric patients 2 to 12 years of age; 5953% were male; and 5247% were White, 2628% were Asian, and 448% were Black or African American; and 19% were Hispanic/Latino. The most common cancers were MTC (5242%), and papillary thyroid cancer (3742%).

Serious adverse reactions occurred in 2242% of patients who received RETEVMO. ~~The s~~Serious adverse reactions occurring (in more than 1 patient each) were abdominal infection, abdominal pain, aspiration, constipation, diarrhea, epiphysiolysis, nausea, pneumonia, pneumatosis intestinalis, rhinovirus infection, sepsis, vomiting and fracture (2 patients each).

Dosage interruptions due to an adverse reaction occurred in 2242% of patients who received RETEVMO. Adverse reactions requiring dosage interruption in ≥5% of patients included increased ALT, increased AST, ascites, increased bilirubin, decreased neutrophils, and pyrexia.

Dose reductions due to an adverse reaction occurred in 4522% of patients who received RETEVMO. Adverse reactions requiring dosage reductions in ≥2% of patients included increased ALT, decreased neutrophils, increased weight, and increased bilirubin.

The most common adverse reactions (≥25%) were musculoskeletal pain, diarrhea, nausea, hemorrhage, pyrexia, abdominal pain, headache, vomiting, fatigue, cough, rash, coronavirus infection, upper respiratory tract infection, and edema.

The most common Grade 3 or 4 laboratory abnormalities (≥5%) were decreased lymphocytes, decreased calcium, decreased hemoglobin, decreased neutrophils, increased ALT, decreased magnesium, and decreased potassium.

Table 7 summarizes the adverse reactions in LIBRETTO-121.

Table 8: Adverse Reactions (≥15%) in Patients Who Received RETEVMO in LIBRETTO-121

Adverse Reactions	RETEVMO N= 2736	
	Grades 1-4# %	Grades 3-4 %
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain ¹	5658	0
Gastrointestinal Disorders		
Diarrhea ²	4147	02.8*
Nausea	3042	2.8*
Abdominal pain ³	2636	0
Vomiting	3031	7.8*
Constipation	1922	6*
Stomatitis	15	0
Blood and Lymphatic System Disorders		
Hemorrhage ⁴	2639	0
General Disorders and Administration Site Conditions		
Pyrexia	2639	0
Fatigue ⁵	2631	0
Edema ⁶	1925	0
Nervous System Disorders		
Headache	33	0
Respiratory, Thoracic and Mediastinal Disorders		
Cough	2231	0
Oropharyngeal pain	22	0
Skin and Subcutaneous Tissue Disorders		
Rash ⁷	1928	0
Infections and Infestations		
Coronavirus infection	28	0
Upper respiratory tract infection	2228	02.8*
Urinary tract infection ⁸	19	2.8*
Endocrine Disorders		
Hypothyroidism ⁹	1922	0
Investigations		
Increased weight	19	7.11*

- 1 Musculoskeletal pain includes arthralgia, back pain, bone pain, musculoskeletal chest pain, non-cardiac chest pain, neck pain, pain in extremity
- 2 Diarrhea includes anal incontinence
- 3 Abdominal pain includes abdominal pain upper, **abdominal discomfort**
- ~~4 Stomatitis includes angular cheilitis~~
- 4 Hemorrhage includes epistaxis, **hematuria, anal hemorrhage, blood urine present, hemoptysis, menorrhagia**, mouth hemorrhage
- 5 Fatigue includes asthenia, malaise
- 6 Edema includes **face edema**, edema peripheral, **face periorbital edema**, localized edema, generalized edema, **gastrointestinal edema**, swelling
- 7 **Rash includes rash maculopapular, rash erythematous, urticaria**
- 8 **Urinary tract infection includes cystitis**
- 9 Hypothyroidism includes blood thyroid stimulating hormone increased, thyroglobulin increased
- * No Grade 4 events were reported.
- # Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Clinically relevant adverse reactions in <15% of patients who received RETEVMO include dizziness (~~11%~~), ~~urinary tract infection (11%)~~, ~~decreased appetite (7.14%)~~, electrocardiogram QT prolonged (~~7.14%~~), hypersensitivity (~~7.11%~~), **stomatitis (14%)**, **proteinuria (11%)**, hypertension (~~7.8%~~), decreased appetite (~~8%~~), **erectile dysfunction (6%)**, **chylous ascites (2.8%)**, **dry mouth (2.8%)**, **epiphysiolysis (2.8%)**, and pneumonia (~~3.7~~2.8%).

Table 8 summarizes the laboratory abnormalities in LIBRETTO-121.

Table 9: Select Laboratory Abnormalities (≥15%) Worsening from Baseline in Patients Who Received RETEVMO in LIBRETTO-121

Laboratory Abnormality	RETEVMO ¹	
	Grades 1-4 [#] (%)	Grades 3-4 (%)
Chemistry		
Decreased calcium	59 61	7 11
Increased ALT	56 58	3.7 8*
Decreased albumin	44 53	0
Increased alkaline phosphatase	50	0
Increased AST	48 50	2.8*
Increased bilirubin	30 31	0 2.8*
Increased cholesterol	28	0
Decreased magnesium	15 28	3.7 6
Increased potassium	28	2.8
Increased creatinine	19	0 2.8
Decreased potassium	19	3.7 6
Decreased sodium	17	0
Hematology		
Decreased neutrophils	40	7 8
Decreased hemoglobin	19 36	7 11*

<u>Increased hemoglobin</u>	<u>33</u>	<u>2.8*</u>
Decreased platelets	<u>2228</u>	<u>02.8*</u>
Decreased lymphocytes	<u>2428</u>	<u>4.814</u>

¹ Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 2418 to 2736 patients.

* No Grade 4 abnormalities were reported.

Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.

[...]

7.2 Postmarketing Experience

The following adverse reaction has been identified during post-approval use of RETEVMO. Because such reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: Stevens-Johnson Syndrome

העדכונים העיקריים בעלון לצרן הינם:

4. תופעות לוואי

[...]

תופעות הלוואי השכיחות ביותר (תופעות שמופיעות ביותר ממשמש אחד מעשרה) של רטבמו בילדים מגיל 12 ומעלה עם גידולים סולידיים כוללות:

- כאבי שרירים ועצמות
- שלשול
- כאב ראש
- בחילה
- הקאה
- שיעול
- זיהום בדרכי נשימה עליונות
- הדבקות בנגיף הקורונה
- כאב באיזור הקיבה (כאב בטן)
- עייפות
- חום
- דימומים
- פריחה
- נפיחות

[...]

תוצאות בדיקות המעבדה החמורות השכיחות ביותר עם רטבמו בילדים מגיל 12 ומעלה עם גידולים סולידיים כוללות ירידה בספירת תאי דם לבנים, ירידה ברמות הסיידן בדם, ירידה בספירת תאי דם אדומים, עלייה באנזימי כבד, ירידה ברמות המגנזיום בדם וירידה ברמות האשלגן בדם.

תופעות לוואי שדווחו לאחר שיווק התרופה:

תופעת הלוואי הבאה זוהתה לאחר אישור רטבמו לשיווק. מאחר שתופעות אלו מדווחות מרצון מתוך אוכלוסייה בגודל לא ידוע, לא תמיד ניתן להעריך את שכיחותן באופן מהימן או לקבוע קשר סיבתי ברור לחשיפה לתרופה.

- הפרעות בעור וברקמה התת-עורית: תסמונת סטיבנס-ג'ונסון (Stevens-Johnson Syndrome).