אוקטובר 2024

רופא/ה נכבד/ה
רוקח/ת נכבד/ה

חברת אלי לילי ישראל מבקשת להודיעכם על אישור התוויה חדשה לטיפול ב- Other *RET* Fusion-Positive Solid Tumors עבור התכשירים:

Retevmo 40 mg	**רטבמו 40 מ"ג**
Retevmo 80 mg	**רטבמו 80 מ"ג**

צורת מינון: Capsules

החומר הפעיל: Selepercatinib

ההתוויות המאושרות לתכשיר בישראל:

•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.

בהודעה זו מצויינים העדכונים העיקריים בעלונים לרופא ולצרכן. קיימים עדכונים נוספים.
טקסט שהתווסף מסומן בכחול בקו תחתון. טקסט שנמחק מסומן בקו חוצה. החמרות מסומנות בצבע צהוב.

העלונים המעודכנים מפורסמים במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפסים על ידי פנייה לבעל הרישום: אלי לילי ישראל בע"מ, השיזף 4, רעננה, טל': 09-9606234.

בברכה,
יצחק תירוש
רוקח ממונה
אלי לילי ישראל בע"מ

להלן העדכונים העיקריים בעלון לרופא:

1 INDICATIONS AND USAGE

1.4 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.

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2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for treatment with RETEVMO based on the presence of a *RET* gene fusion (NSCLC ~~or~~ thyroid cancer, or other solid tumors) or specific *RET* gene mutation (MTC) in tumor specimens ~~or plasma~~ *[see Clinical Studies (14)]*.

5 WARNINGS AND PRECAUTIONS

5.11 Slipped Capital Femoral Epiphysis/Slipped Upper Femoral Epiphysis in Pediatric Patients

Slipped capital femoral epiphysis/slipped upper femoral epiphysis (SCFE/SUFE) occurred in 1 adolescent (3.7% of 27 patients) receiving RETEVMO in LIBRETTO-121 and 1 adolescent (0.5% of 193 patients) receiving RETEVMO in LIBRETTO-531 *[see Adverse Reactions (6.1)]*. Monitor patients for symptoms indicative of SCFE/SUFE and treat as medically and surgically appropriate *[see Adverse Reactions (6.1)]*.

6.1 Clinical Trials Experience

[…]

Treatment-naïve RET Fusion-Positive Non-small Cell Lung Cancer

LIBRETTO-431

The safety population described below reflects exposure to RETEVMO as a single agent administered at 160 mg orally twice daily evaluated in 158 patients with unresectable locally advanced or metastatic *RET* fusion-positive NSCLC in LIBRETTO-431 [see Clinical Studies (14)].
Among the 158 patients who received RETEVMO, the median duration of exposure was 16.7 months (range: 5 days to 37.9 months); 87% were exposed for 6 months or longer and 70% were exposed for one year or longer.
The median age was 61 years (range: 31 to 87 years); 46% were male; and 36% were White, 58% were Asian, 1.3% were Black or African American, 1.3% were American Indian or Alaska Native, and 3.2% were missing.
Serious adverse reactions occurred in 35% of patients who received RETEVMO. The most frequent serious adverse reactions (≥2% of patients) were pleural effusion, and abnormal hepatic function.
Fatal adverse reactions occurred in 4.4% of patients who received RETEVMO; fatal adverse reactions included myocardial infarction (n = 2), respiratory failure (n = 2), cardiac arrest, malnutrition, and sudden death (n = 1, each).
Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received RETEVMO. Adverse reactions resulting in permanent discontinuation in ≥1% of patients included increased ALT (1.3%), and myocardial infarction (1.3%).
Dosage interruptions due to an adverse reaction occurred in 72% of patients who received RETEVMO. Adverse reactions requiring dosage interruption in ≥5% of patients included increased ALT, hypertension, increased AST, QT prolongation, diarrhea, and COVID-19 infection.
Dose reductions due to an adverse reaction occurred in 51% of patients who received RETEVMO. Adverse reactions requiring dose reductions in ≥5% of patients included increased ALT, increased AST, QT prolongation.
The most common adverse reactions (≥25%) in patients who received RETEVMO were hypertension, diarrhea, edema, dry mouth, rash, fatigue, abdominal pain, and musculoskeletal pain.
The most common Grade 3 or 4 laboratory abnormalities (≥5%) in patients who received RETEVMO were increased ALT, increased AST, and decreased lymphocytes.
Table 9 summarizes the adverse reactions in LIBRETTO-431.

Table 9: Adverse Reactions (≥15%) in Patients on Either Arm in LIBRETTO-431

Adverse Reaction	RETEVMO (n=158)		Chemotherapy with or without pembrolizumab (n=98)	
	Grades 1-4# (%)	Grades 3-4 (%)	Grades 1-4# (%)	Grades 3-4 (%)
Vascular disorders				
Hypertension	48	20*	7	3.1*
Gastrointestinal disorders				
Diarrhea[1]	44	1.3*	24	2.0*
Dry mouth[2]	39	0	6	0
Abdominal pain[3]	25	0.6*	19	2.0*
Constipation	22	0	40	1.0*
Stomatitis[4]	18	0	16	0
Nausea	13	0	44	1.0*
Vomiting[5]	13	0	23	1.0*
General disorders and administration site conditions				
Edema[6]	41	2.5*	28	0
Fatigue[7]	32	3.2*	50	5*
Pyrexia	13	0.6*	23	0
Skin and subcutaneous tissue disorders				
Rash[8]	33	1.9*	30	1.0*
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[9]	25	0	28	0
Investigations				
Electrocardiogram QT prolonged	20	9*	1.0	0
Infections and infestations				
COVID-19 infection	19	0.6*	18	0
Metabolism and nutrition disorders				
Decreased appetite	17	0	34	2.0*

[1] Diarrhea includes diarrhea, anal incontinence.

[2] Dry mouth includes dry mouth, mucosal dryness.

[3] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, gastrointestinal pain.

[4] Stomatitis includes stomatitis, mouth ulceration, mucosal inflammation.

[5] Vomiting includes vomiting, retching, regurgitation.

[6] Edema includes edema, edema peripheral, face edema, periorbital edema, swelling face, peripheral swelling, localized edema, eyelid edema, orbital edema, eye edema, scrotal edema, penile edema, orbital swelling, periorbital swelling.

[7] Fatigue includes fatigue, asthenia, malaise.

[8] Rash includes rash, rash maculopapular, skin exfoliation, rash erythematous, rash macular, dermatitis, urticaria, rash papular, dermatitis allergic, rash pustular, rash vesicular, genital rash.

[9] Musculoskeletal pain includes musculoskeletal pain, arthralgia, back pain, bone pain, musculoskeletal chest pain, non-cardiac chest pain, neck pain, pain in extremity.

* No Grade 4 abnormalities 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 headache (14%); hemorrhage (13%); urinary tract infections (12%); hypothyroidism (9%); pneumonia (9%); dizziness (8%); interstitial lung disease/pneumonitis (4.4%); hypersensitivity, chylous ascites, and chylothorax (all < 2%).

Table 10 summarizes the laboratory abnormalities in LIBRETTO-431.

Table 10: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients on Either Arm in LIBRETTO-431

Laboratory Abnormality[1]	RETEVMO		Chemotherapy with or without pembrolizumab	
	Grades 1-4# (%)	Grades 3-4 (%)	Grades 1-4# (%)	Grades 3-4 (%)
Chemistry				
ALT increased	81	21	63	4.1
AST increased	77	10	46	0
Alkaline phosphatase Increased	35	1.3	22	0
Total bilirubin Increased	52	1.3	9	0
Blood creatinine Increased	23	0	21	0
Magnesium decreased	16	0.6	8	0
Albumin decreased	25	0	5	0
Calcium decreased	53	1.9	24	1.0
Sodium decreased	31	3.2	41	2.1
Potassium decreased	17	1.3	15	1.0
Hematology				
Platelets decreased	53	3.2	39	5
Lymphocyte count decreased	53	8	64	15
Hemoglobin decreased	21	0	91	5
Neutrophil count decreased	53	2.0	58	11

[1] Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available: RETEVMO (range: 154 to 157 patients) and chemotherapy with or without pembrolizumab (range: 96 to 97 patients).

Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Increased Creatinine

In healthy subjects administered RETEVMO 160 mg orally twice daily, serum creatinine increased 18% after 10 days. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed *[see Clinical Pharmacology (12.3)]*.

RET-Mutant Medullary Thyroid Cancer

LIBRETTO-531

The safety population described below reflects exposure to RETEVMO as a single agent administered at 160 mg (adults) or at 92 mg/m^2 (adolescent, not to exceed 160 mg) orally twice daily, in patients with progressive, advanced, kinase inhibitor naïve, *RET*-mutant medullary thyroid cancer in LIBRETTO-531 *[see Clinical Studies (14.2)]*. Among the 193 patients who received RETEVMO, the observed median duration of exposure was 14.5 months (range: 25 days to 36 months); 80% were exposed for 6 months or longer and 59% were exposed for one year or longer.

The median age was 55 years (range: 12 to 84 years); 63% were male; and 69% were White, 28% were Asian, 2.9% were Black or African American and ethnicity was not routinely collected.
Serious adverse reactions occurred in 22% of patients who received RETEVMO. The most frequent serious adverse reactions were pneumonia and pyrexia (n = 3, each) and hypertension and urinary tract infection (n = 2, each). Fatal adverse reactions occurred in 2.1% of patients; fatal adverse reactions included COVID-19, diabetic ketoacidosis, multiple organ dysfunction syndrome, and sudden death (n=1 each).
Permanent discontinuation due to an adverse reaction occurred in 4.7% of patients who received RETEVMO. Adverse reactions resulting in permanent discontinuation were edema, multiple organ

dysfunction syndrome, sudden death, AST increased, diabetic ketoacidosis, chronic kidney disease, retinopathy, COVID-19, and somatic symptom disorder (n = 1, each).
Dosage interruptions due to an adverse reaction occurred in 49% of patients who received RETEVMO. Adverse reactions requiring dosage omission in ≥5% of patients included ALT increased (9%) and hypertension (7%).
Dose reductions due to an adverse reaction occurred in 39% of patients who received RETEVMO. One adverse reaction, increased ALT (7%), required a dose reduction in ≥5% of patients.
The most common adverse reactions (≥25%) in patients who received RETEVMO were hypertension, edema, dry mouth, fatigue, and diarrhea.
The most common Grade 3 or 4 laboratory abnormalities (≥5%) in patients who received RETEVMO were decreased lymphocytes, increased ALT, decreased neutrophils, increased ALP, increased blood creatinine, decreased calcium, and increased AST.
Table 11 summarizes the adverse reactions in LIBRETTO-531.

Table 11: Adverse Reactions (≥10%) in Patients Who Received RETEVMO in LIBRETTO-531

Adverse Reaction	RETEVMO N = 193		Cabozantinib or Vandetanib N = 97	
	Grades 1-4# (%)	Grades 3-4 (%)	Grades 1-4# (%)	Grades 3-4 (%)
Vascular disorders				
Hypertension[1]	43	19*	41	18*
General disorders and administration-site conditions				
Edema[2]	33	0	5	0
Fatigue[3]	28	4.1*	47	9*
Pyrexia	12	1.0*	2.1	0
Gastrointestinal disorders				
Dry mouth[4]	32	0.5*	10	1.0*
Diarrhea[5]	26	3.1*	61	8*
Abdominal pain[6]	18	0.5*	21	2.1*
Constipation	16	0	12	0
Stomatitis[7]	14	0.5*	42	13*
Pyrexia	12	1.0*	2.1	0
Nausea	10	1.0*	32	5*
Nervous system disorders				
Headache[8]	23	0.5*	21	0
Skin and subcutaneous tissue disorders				
Rash[9]	19	1.6*	27	4.1*
Reproductive system and breast disorders				
Erectile dysfunction	16	0	0	0
Investigations				
Electrocardiogram QT prolonged[10]	14	4.7*	13	2.1*
Metabolism and nutrition disorders				
Decreased appetite	12	0.5*	28	5*
Endocrine disorders				
Hypothyroidism[11]	11	0	21	0

1 Hypertension includes hypertension, blood pressure increased.

2 Edema includes edema peripheral, face edema, periorbital edema, swelling face, peripheral swelling, localized edema, eyelid edema, generalized edema, eye swelling, lymphoedema, orbital edema, eye edema, edema, edema genital, swelling, scrotal edema, scrotal swelling, angioedema, skin edema, testicular swelling, vulvovaginal swelling.

3 Fatigue includes fatigue, asthenia, malaise.

4 Dry mouth includes dry mouth, mucosal dryness.

5 Diarrhea includes diarrhea, anal incontinence, defecation urgency, frequent bowel movements, gastrointestinal hypermotility.

6 Abdominal pain included abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, gastrointestinal pain.

7 Stomatitis includes stomatitis, mouth ulceration, mucosal inflammation.

8 Headache includes headache, sinus headache, tension headache.

9 Rash includes rash, rash maculopapular, skin exfoliation, rash erythematous, rash macular, dermatitis, urticaria, rash pruritic, exfoliative rash, rash papular, dermatitis allergic, rash follicular, rash generalized, rash pustular, butterfly rash, rash morbilliform, rash vesicular.

10 Electrocardiogram QT prolongation includes electrocardiogram QT prolonged, electrocardiogram QT interval abnormal.

11 Hypothyroidism includes hypothyroidism, blood thyroid stimulating hormone increased.

* Only includes a Grade 3 adverse reaction

Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0.

Clinically relevant adverse reactions in ≤10% of patients who received RETEVMO include dizziness (8%); urinary tract infections (8%); vomiting (8%); pneumonia, interstitial lung disease/pneumonitis, chylous ascites and hypersensitivity (all < 2%).
Table 12 summarizes the laboratory abnormalities in LIBRETTO-531.

Table 12: Select Laboratory Abnormalities (≥5%) Worsening from Baseline in Patients Who Received RETEVMO in LIBRETTO-531

Laboratory Abnormality	RETEVMO[1]		Cabozantinib or Vandetanib[1]	
	Grades 1-4[#] %	Grades 3-4 %	Grades 1-4[#] %	Grades 3-4 %
Chemistry				
Calcium decreased	55	5	62	11
ALT increased	53	16	72	7*
AST increased	47	5	68	3.2*
Alkaline phosphatase increased	37	6	28	5
Total bilirubin increased	32	1.1	30	3.2*
Blood creatinine increased	27	6	16	8
Sodium decreased	20	3.2*	16	0
Albumin decreased	11	1.1	7	0
Magnesium decreased	9	3.3	26	9
Potassium decreased	8	0	22	4.4*
Hematology				
Lymphocyte count decreased	41	18	36	13
Neutrophil count decreased	33	14	42	19
Platelets decreased	28	1.1	34	1.1*
Hemoglobin decreased	18	2.1*	23	2.1*

1 Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available: RETEVMO (range: 183 to 191 patients) and chemotherapy with or without cabozantinib or vandetanib (range: 91 to 94 patients).

* Only includes a Grade 3 laboratory abnormality

Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0

להלן העדכונים העקריים בעלון לצרכן:

1. למה מיועדת התרופה?

רטבמו משמשת לטיפול בסוגי סרטן מסוימים הנגרמים על ידי מופעים חריגים של גנים מסוג RET ומיועדת:

[...]

- כטיפול יחיד במבוגרים עם גידולים סולידיים מתקדמים חיוביים ל-RET Fusion, כאשר אפשרויות הטיפול שאינן מכוונות ל-RET מספקות תועלת קלינית מוגבלת, או שכבר מוצו.

4. תופעות לוואי

תופעות לוואי נוספות

תופעות הלוואי השכיחות ~~מאוד~~ ביותר (≥25%) של רטבמו במבוגרים עם גידולים סולידיים ~~(עלולות להשפיע על יותר ממשתמש 1 מתוך 10)~~ כוללות:

- נפיחות בזרועות, רגליים, ידיים וכפות הרגליים (בצקת פריפריאלית)
- שלשול
- עייפות
- יובש בפה
- לחץ דם גבוה
- כאב בטן
- עצירות
- פריחה
- בחילה
- כאב ראש

תופעות הלוואי השכיחות ביותר (≥25%) של רטבמו בילדים מגיל 12 ומעלה עם גידולים סולידיים כוללות:

- כאבי שרירים ועצמות
- שלשול
- כאב ראש
- בחילה
- הקאה
- הדבקות בנגיף הקורונה
- כאב בטן
- עייפות
- חום
- דימומים

תוצאות בדיקות המעבדה החמורות השכיחות ביותר עם רטבמו במבוגרים עם גידולים סולידיים כוללות ירידה בספירת תאי דם לבנים, עלייה באנזימי כבד, ירידה ברמות הנתרן בדם וירידה ברמות הסידן בדם.

תוצאות בדיקות המעבדה החמורות השכיחות ביותר עם רטבמו בילדים מגיל 12 ומעלה עם גידולים סולידיים כוללות
ירידה ברמות הסידן בדם, ירידה בספירת תאי דם אדומים וירידה בספירת תאי דם לבנים.

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