אוגוסט 2024

רופא/ה נכבד/ה,

רוקח/ת נכבד/ה,

<u>הנדון: לנווימה 4 מ"ג, 10 מ"ג- Lenvima 4 mg, 10mg, Hard Capsule</u>

חברת אסאיי ישראל בע"מ (Eisai Israel Ltd.) מבקשת להודיעכם כי העלונים לרופא ולצרכן של התכשירים שלהלן התעדכנו ביוני 2024.

Lenvima 4 mg
Lenvima 10mg

פרטי העדכון העיקריים מופיעים בהמשך (טקסט שנוסף מסומן באדום, טקסט שהושמט מסומן בטקסט ~~אדום עם קו חוצה~~).

ההתוויות המאושרות לתכשיר בישראל:

LENVIMA is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC) refractory to radioactive iodine (RAI).
LENVIMA is indicated in combination with everolimus for the treatment of adult patients with advanced clear cell renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.
LENVIMA is indicated as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy.
Lenvima, in combination with pembrolizumab, is indicated for the treatment of adult patients with advanced or recurrent endometrial carcinoma who have disease progression on or following prior treatment with a platinum containing therapy and who are not candidates for curative surgery or radiation.
LENVIMA is indicated in combination with pembrolizumab for the first-line treatment of adult patients with advanced RCC.

העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות ומצורפים לפרסום זה. כמו כן, ניתן לקבל העתקים מודפסים באמצעות פנייה לבעל הרישום: אסאיי ישראל בע"מ, ת.ד. 8049 כפר סבא, 4418001.

להלן העדכונים בעלון לרופא:

4.8 Undesirable effects

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Table 7 Adverse reactions reported in patients treated with lenvatinib

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System Organ Class (MedDRA terminology)	**Lenvatinib monotherapy**	**Combination with everolimus**	**Combination with pembrolizumab (RCC)**	**Combination with pembrolizumab (EC)**
Gastrointestinal disorders				
Common	Anal fistula Flatulence Gastrointestinal perforation	Dry mouth Flatulence Gastrointestinal perforation	Pancreatitis[g] Colitis Flatulence Gastrointestinal perforation	Pancreatitis[i] Flatulence Dyspepsia Colitis Gastrointestinal perforation

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Paediatric population

In the paediatric Studies 207, 216, 230, and ~~230~~ 231 (see section 5.1), the overall safety profile of lenvatinib as a single agent or in combination with either ifosfamide and etoposide or everolimus was consistent with that observed in adults treated with lenvatinib.

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~~No patient discontinued study treatment due to pneumothorax.~~ In Study 216, pneumothorax was reported in 3 patients (4.7%) with Ewing sarcoma, rhabdomyosarcoma (RMS) and Wilms tumour; all 3 patients had lung metastases at baseline. In Study 231, pneumothorax was reported in 7 patients (5.5%) with spindle cell sarcoma, undifferentiated sarcoma, RMS, malignant peripheral nerve sheath tumour, synovial sarcoma, spindle cell carcinoma, and malignant fibromyxoid ossifying tumour; all 7 patients had lung metastases or primary disease in the chest wall or pleural cavity at baseline. For Studies 216, 230, and 231, no patient discontinued study treatment due to pneumothorax. Pneumothorax occurrence appeared to be mainly associated with pulmonary metastases and underlying disease.

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In Phase 1 (combination dose-finding cohort) of Study 216, the most frequently (≥40%) reported adverse drug reactions were hypertension, hypothyroidism, hypertriglyceridemia, abdominal pain, and diarrhoea; and in Phase 2 (combination expansion cohort), the most frequently reported (≥35%) adverse drug reactions were hypertriglyceridemia, proteinuria, diarrhoea, lymphocyte count decreased, white blood cell count decreased, blood cholesterol increased, fatigue, and platelet count decreased.

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In Study 231, the most frequently reported (≥15%) adverse drug reactions were hypothyroidism, hypertension, proteinuria, decreased appetite, diarrhoea, and platelet count decreased.

5.1 Pharmacodynamic properties

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Open-label, single arm Phase 2 study

Additional data are available from the open-label, single-arm, Phase 2 study KEYNOTE-B61 of lenvatinib (20 mg OD) in combination with pembrolizumab (400 mg every 6 weeks) for the first-line treatment of patients with advanced or metastatic RCC with non-clear cell histology (n=158), including 59% papillary, 18% chromophobe, 4% translocation, 1% medullary, 13% unclassified, and 6% other. The ORR was 50.6% (95% CI (42.6, 58.7)), and the median duration of response was 19.5 months (95% CI 15.3, NR).

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Study 216 was a multicentre, open-label, single-arm, Phase 1/2 study to determine the safety, tolerability,

and antitumour activity of lenvatinib administered in combination with everolimus in paediatric patients (and young adults aged ≤21 years) with relapsed or refractory solid malignancies, including CNS tumours. A total of 64 patients were enrolled and treated. In Phase 1 (combination dose-finding), 23 patients were enrolled and treated: 5 at Dose Level –1 (lenvatinib 8 mg/m2 and everolimus 3 mg/m2) and 18 at Dose Level 1 (lenvatinib 11 mg/m2 and everolimus 3 mg/m2). The recommended dose (RD) of the combination was lenvatinib 11 mg/m2 and everolimus 3 mg/m2, taken once daily. In Phase 2 (combination expansion), 41 patients were enrolled and treated at the RD in the following cohorts: Ewing Sarcoma (EWS, n=10), Rhabdomyosarcoma (RMS, n=20), and High-grade glioma (HGG, n=11). The primary efficacy outcome measure was objective response rate (ORR) at Week 16 in evaluable patients based on investigator assessment using RECIST v1.1 or RANO (for patients with HGG). There were no objective responses observed in the EWS and HGG cohorts; 2 partial responses (PRs) were observed in the RMS cohort for an ORR at Week 16 of 10% (95% CI: 1.2, 31.7).

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Study 231 is a multicentre, open-label, Phase 2 basket study to evaluate the antitumour activity and safety of lenvatinib in children, adolescents, and young adults between 2 to ≤21 years of age with relapsed or refractory solid malignancies, including EWS, RMS, and HGG. A total of 127 patients were enrolled and treated at the lenvatinib RD (14 mg/m2) in the following cohorts: EWS (n=9), RMS (n=17), HGG (n=8), and other solid tumours (n=9 each for diffuse midline glioma, medulloblastoma, and ependymoma; all other solid tumours n=66). The primary efficacy outcome measure was ORR at Week 16 in evaluable patients based on investigator assessment using RECIST v1.1 or RANO (for patients with HGG). There were no objective responses observed in patients with HGG, diffuse midline glioma, medulloblastoma, or ependymoma. Two PRs were observed in both the EWS and RMS cohorts for an ORR at Week 16 of 22.2% (95% CI: 2.8, 60.0) and 11.8% (95% CI: 1.5, 36.4), respectively. Five PRs (in patients with synovial sarcoma [n=2], kaposiform hemangioendothelioma [n=1], Wilms tumour nephroblastoma [n=1], and clear cell carcinoma [n=1]) were observed among all other solid tumours for an ORR at Week 16 of 7.7% (95% CI: 2.5, 17.0).

5.2 Pharmacokinetic properties

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Paediatric Population

Based on a population pharmacokinetics analysis in paediatric patients of 2 to 12 years old ~~on pooled data from 1100 paediatric, adolescent and adult subjects~~, which included data from 3 paediatric patients aged 2 to <3 years, 28 paediatric patients aged ≥3 to <6 years and 89 paediatric patients aged 6 to ≤12 years across the lenvatinib paediatric program, lenvatinib oral clearance (CL/F) was affected by body weight but not age.

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להלן העדכונים בעלון לצרכן:

4. תופעות לוואי:

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תופעות הלוואי הבאות עלולות להופיע עם השימוש בלנווימה בטיפול יחיד:

תופעות לוואי שכיחות מאוד: (משפיעות על יותר מ-1 מתוך 10 מטופלים)

- …
- תת פעילות של בלוטת התריס (עייפות, עלייה במשקל, עצירות, תחושת קור, עור יבש) ושינוי בתוצאות בדיקות דם ברמת ההורמון המגרה של בלוטת התריס (TSH) (גבוהה)

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תופעות הלוואי הבאות עלולות להופיע בשילוב של לנווימה עם אברולימוס:

תופעות לוואי שכיחות מאוד: (משפיעות על יותר מ-1 מתוך 10 מטופלים)

- …

- תת פעילות של בלוטת התריס (עייפות, עלייה במשקל, עצירות, תחושת קור, עור יבש) ושינויים בתוצאות בדיקת דם עבור ההורמון המגרה של בלוטת התריס (TSH) (רמות גבוהות)

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תופעות לוואי שכיחות: (משפיעות על עד 1 מתוך 10 מטופלים)

- ...
- ניקוב (פרפורציה) של הקיבה או המעיים

<u>תופעות הלוואי הבאות עלולות להופיע בשילוב של לנווימה עם פמברוליזומב לטיפול בסרטן כליה מתקדם:</u>

תופעות לוואי שכיחות: (משפיעות על עד 1 מתוך 10 מטופלים)

- ...
- ניקוב (פרפורציה) של הקיבה או המעיים

בברכה,

אלינה ורמן, רוקחת ממונה

אסאיי ישראל בע"מ