מרץ 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 בפברואר 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:

4.2 Posology and method of administration

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<u>Paediatric population</u>

The safety and efficacy of lenvatinib in children aged 2 to <18 years have not been established. Currently available data are described in sections 4.8, 5.1, and 5.2 but no recommendation on a

posology can be made.
Lenvatinib should not be used in children younger than 2 years of age because of safety concerns identified in animal studies (see section 5.3). ~~The safety and efficacy of lenvatinib in children aged 2 to <18 years have not yet been established (see section 5.1). No data are available.~~

4.8 Undesirable effects

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

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Paediatric population

In the paediatric Studies 207 and 230 (see section 5.1), the overall safety profile of lenvatinib as a single agent or in combination with ifosfamide and etoposide was consistent with that observed in adults treated with lenvatinib. In patients with relapsed/refractory osteosarcoma, pneumothorax was reported at a frequency higher than that observed in adults with DTC, HCC, RCC and EC. In Study 207, pneumothorax occurred in 6 patients (10.9%) treated with single -agent lenvatinib and 7 patients (16.7%) treated with lenvatinib in combination with ifosfamide and etoposide. Overall, 2 patients discontinued study treatment due to pneumothorax. In Study 230, pneumothorax was reported in 12 patients (11 patients [28.2%] treated with lenvatinib plus ifosfamide and etoposide, and 1 patient [2.6%] treated with ifosfamide and etoposide). No patient discontinued study treatment due to pneumothorax. Pneumothorax occurrence appeared to be mainly associated with pulmonary metastases and underlying disease.
In the single-agent dose-finding cohort of Study 207, the most frequently (≥40%) reported adverse drug reactions were decreased appetite, diarrhoea, hypothyroidism, vomiting, abdominal pain, pyrexia, hypertension, and weight decreased; and in the single-agent expansion cohort of patients with relapsed or refractory osteosarcoma, the most frequently (≥40%) reported adverse drug reactions were decreased appetite, headache, vomiting, hypothyroidism, and proteinuria.
In the combination dose-finding cohort of Study 207, the most frequently (≥50%) reported adverse drug reactions were vomiting, anaemia, nausea, diarrhoea, hypothyroidism, abdominal pain, arthralgia, epistaxis, neutropenia, constipation, headache, and pain in extremity; and in the combination expansion cohort, the most frequently (≥50%) reported adverse drug reactions were anaemia, nausea, white blood cell count decreased, diarrhoea, vomiting, and platelet count decreased.
In the OLIE study (Study 230), the most frequently (≥35%) reported adverse drug reactions were hypothyroidism, anaemia, nausea, platelet count decreased, proteinuria, vomiting, back pain, febrile neutropenia, hypertension, constipation, diarrhoea, neutrophil count decreased, and pyrexia. ~~See~~

~~section 4.2 for information on paediatric use.~~

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5.1 Pharmacodynamic properties

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Paediatric population

Paediatric studies

The efficacy of lenvatinib was assessed but not established in two open-label studies:
Study 207 was a Phase 1/2, open-label, multi-centre, dose-finding and activity-estimating study of lenvatinib as a single agent and in combination with ifosfamide and etoposide in paediatric patients (aged 2 to <18 years; 2 to ≤25 years for osteosarcoma), with relapsed or refractory solid tumours. A total of 97 patients were enrolled. In the lenvatinib single agent dose-finding cohort, 23 patients were enrolled and received lenvatinib orally, once daily, across 3 dose levels (11, 14, or 17 mg/m2). In the lenvatinib in combination with ifosfamide and etoposide dose-finding cohort, a total of 22 patients were enrolled and received lenvatinib across 2 dose levels (11 or 14 mg/m2). The recommended dose (RD) of lenvatinib as a single agent, and in combination with ifosfamide and etoposide was determined as 14 mg/m2 orally, once daily.
In the lenvatinib single agent expansion cohort of relapsed or refractory DTC, the primary efficacy outcome measure was objective response rate (ORR; complete response [CR] + partial response [PR]). One patient was enrolled, and this patient achieved a PR. In both the lenvatinib single agent, and combination with ifosfamide and etoposide expansion cohorts of relapsed or refractory osteosarcoma, the primary efficacy outcome measure was progression-free survival rate at 4 months (PFS-4); the PFS-4 by binomial estimate including all 31 patients treated with lenvatinib as a single agent was 29% (95%CI: 14.2, 48.0); the PFS-4 by binomial estimate in all 20 patients treated in the lenvatinib in combination with ifosfamide and etoposide expansion cohort was 50% (95%CI: 27.2, 72.8).
The OLIE study (Study 230) was a Phase 2, open-label, multi-centre, randomized, controlled trial in patients (aged 2 to ≤25 years) with relapsed or refractory osteosarcoma. A total of 81 patients were randomized in a 1:1 ratio (78 treated; 39 in each arm) to lenvatinib 14 mg/m2 in combination with ifosfamide 3000 mg/m2 and etoposide 100 mg/m2 (Arm A) or ifosfamide 3000 mg/m2 and etoposide 100 mg/m2 (Arm B). Ifosfamide and etoposide were administered intravenously on Days 1 to 3 of each 21-day cycle for a maximum of 5 cycles. Treatment with lenvatinib was permitted until RECIST v1.1-defined disease progression as verified by Blinded Independent Central Review (BICR) or unacceptable toxicity. The primary efficacy outcome measure was progression-free survival (PFS) per RECIST 1.1 by BICR. The trial did not demonstrate a statistically significant difference in median PFS: 6.5 months (95%CI: 5.7, 8.2) for lenvatinib in combination with ifosfamide and etoposide versus 5.5 months (95%CI: 2.9, 6.5) for ifosfamide and etoposide (HR=0.54 [95%CI: 0.27, 1.08]).

5.2 Pharmacokinetic properties

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Paediatric Population

Based on a population pharmacokinetics analysis 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. Predicted exposure levels in terms of area under the curve at steady-state (AUCss) in paediatric patients receiving 14 mg/m2 were comparable to those in adult patients receiving a fixed dose of 24 mg. In these studies, there were no apparent differences in the pharmacokinetics of active substance lenvatinib among children (2 – 12 years), adolescents, and young adult patients with studied tumour types, but data in children are relatively limited to draw definite conclusions (see section 4.2). ~~Paediatric patients have not been studied.~~

להלן העדכונים בעלון לצרכן:

2. **<u>לפני השימוש בתרופה:</u>**

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ילדים ומתבגרים:

התרופה אינה מומלצת לשימוש בילדים ומתבגרים. ~~השפעות התרופה על אנשים~~ מתחת לגיל 18 ~~אינן ידועות~~.

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4. <u>תופעות לוואי:</u>

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<u>תופעות הלוואי הבאות עלולות להופיע עם השימוש בלנווימה בטיפול יחיד:</u>

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

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

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<u>תופעות לוואי שעלולות להופיע בשילוב של לנווימה עם פמברוליזומב לטיפול בסרטן מתקדם או חוזר של רירית הרחם:</u>

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

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

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בברכה,

אלינה ורמן, רוקחת ממונה

אסאיי ישראל בע"מ