LENVATA® CAPSULE

LENVATA®
LENVATINIB

LENVATA® (LENVATINIB) CAPSULE FOR ORAL USE
Read this patient information carefully before you start taking Lenvata® because it answers some common questions about Lenvata®. This medication is prescribed for your current condition, therefore do not use it in similar cases and do not recommend it to others.
To report SUSPECTED ADVERSE REACTIONS, contact Noavaran Daroui Kimia Co. at +982166433514 or send email to medical@kimia-pharma.co

Read this patient information carefully before you start taking Lenvata® because it contains important information for you. This leaflet does not take the place of talking with your healthcare provider about your medical condition or treatment.

Composition
Each capsule Lenvata® 4 mg contains: Lenvatinib (as mesylate) 4 mg.
Each capsule Lenvata® 10 mg contains: Lenvatinib (as mesylate) 10 mg.

Mechanism of action
Lenvatinib is a kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors.

Pharmacokinetic
Absorption
The time to peak plasma concentration (T_{max}) typically occurred from 1 to 4 hours post-dose.
Distribution
Mean steady state volume of distribution is 97 L (%CV, 30.2%). Protein binding of Lenvata® is 97% to 99%.
Metabolism
The main metabolic pathways for Lenvata® in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes.
Excretion
Ten days after a single administration of radiolabeled Lenvata®, approximately 64% and 25% of the radiolabel were eliminated in the feces and urine, respectively.
Elimination
The terminal elimination half-life of Lenvata® was approximately 28 hours.

Indication
Lenvata® is a kinase inhibitor that is indicated:
- For the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC).
- in combination with pembrolizumab, for the first line treatment of adult patients with advanced renal cell carcinoma (RCC) .
- in combination with everolimus, for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior antiangiogenic therapy.
- for the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC).
- In combination with pembrolizumab, for the treatment of patients with advanced endometrial carcinoma (EC) that is mismatch repair proficient (pMMR), as determined by an FDA-approved test, or not microsatellite instability-high (MSI-H), who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

It is not known if Lenvata® is safe and effective in children.

Dosage and Administration
Single agent therapy:
- DTC: The recommended dosage is 24 mg orally once daily.
- HCC: The recommended dosage is based on actual body weight: 12 mg orally once daily for patients greater than or equal to 60 kg or 8 mg orally once daily for patients less than 60 kg.

Combination therapy:
- EC: The recommended dosage is 20 mg orally once daily in combination with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks.
- RCC: The recommended dosage is:
  - 20 mg orally once daily with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks.
  - 18 mg orally once daily with everolimus 5 mg orally once daily.

Modify the recommended daily dose for certain patients with renal or hepatic impairment.

Side effects / Adverse reactions
It should be noted that these side effects do not occur in all patients. These are not all the possible side effects of Lenvata®. For more information, ask your healthcare provider or pharmacist.
Lenvata® may cause serious side effects, including:

- **High blood pressure (hypertension).** High blood pressure is a common side effect of Lenvata® and can be serious. Your healthcare provider should check your blood pressure regularly before and during treatment with Lenvata®. If you develop blood pressure problems, your healthcare provider may prescribe medicine to treat your high blood pressure.
- **Heart problems.** Lenvata® can cause serious heart problems that may be life-threatening. Call your healthcare provider right away if you get symptoms of heart problems, such as shortness of breath or swelling of your ankles.
- **Problem with blood clots in your blood vessels (arteries).** Get emergency medical help right away if you get any of the following symptoms:
  - severe chest pain or pressure
  - numbness or weakness on one side of your body
  - trouble talking
  - sudden vision changes
  - pain in your arms, back, neck or jaw
  - shortness of breath
  - sudden severe headache
- **Liver problems.** Lenvata® may cause liver problems that may lead to liver failure and be life-threatening. Your healthcare provider will check your liver function before and during treatment with Lenvata®. Tell your healthcare provider right away if you have any of the following symptoms:
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark "tea colored" urine
  - light-colored bowel movements (stools)
  - feeling drowsy, confused or loss of consciousness
- **Kidney problems.** Kidney failure, which can be life-threatening, has happened with Lenvata® treatment. Your healthcare provider should do regular blood tests to check your kidneys.
- **Increased protein in your urine (proteinuria).** Proteinuria is a common side effect of Lenvata® and can be serious. Your healthcare provider should check your urine for protein before and during your treatment with Lenvata®.
- **Diarrhea.** Diarrhea is a common side effect of Lenvata® and can be serious. If you get diarrhea, ask your healthcare provider about what medicines you can take to treat your diarrhea. It is important to drink more water when you get diarrhea. Tell your healthcare provider or go to the emergency room, if you are unable to drink enough liquids and your diarrhea is not able to be controlled.
- **An opening in the wall of your stomach or intestines (perforation) or an abnormal connection between two or more body parts (fistula).** Get emergency medical help right away if you have severe stomach (abdomen) pain.
- **Changes in the electrical activity of your heart called QT prolongation.** QT prolongation can cause irregular heartbeats that can be life-threatening. Your healthcare provider will do blood tests before and during your treatment with Lenvata® to check the levels of potassium, magnesium, and calcium in your blood, and may check the electrical activity of your heart with an ECG.
- **Low levels of blood calcium (hypocalcemia).** Your healthcare provider will check your blood calcium levels during treatment with Lenvata® and may tell you to take a calcium supplement if your calcium levels are low.
- **A condition called Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** Call your healthcare provider right away if you get severe headache, seizures, weakness, confusion, or blindness or change in vision.
- **Bleeding.** Lenvata® may cause serious bleeding problems that may be life-threatening. Tell your healthcare provider if you have any signs or symptoms of bleeding during treatment with Lenvata®, including:
  - severe and persistent nose bleeds
  - vomiting blood
  - red or black (looks like tar) stools
  - blood in your urine
  - coughing up blood or blood clots
  - heavy or new onset vaginal bleeding
- **Change in thyroid hormone levels.** Your healthcare provider should check your thyroid hormone levels before starting and every month during treatment with Lenvata®.
- **Wound healing problems.** Wound healing problems have happened in some people who take Lenvata®. Tell your healthcare provider if you plan to have any surgery before or during treatment with Lenvata®.
  - You should stop taking Lenvata® at least 1 week before planned surgery.
  - Your healthcare provider should tell you when you may start taking Lenvata® again after surgery.
- **Severe jaw bone problems (osteonecrosis).** Certain risk factors such as taking a bisphosphonate medicine or the medicine denosumab, having dental disease, or an invasive dental procedure may increase your risk of getting jaw bone problems. Your healthcare provider should examine your mouth before you start and during treatment with Lenvata®. Tell your dentist that you are taking Lenvata®. It is important for you to practice good mouth care during treatment with Lenvata®. Tell your healthcare provider right away if you get signs or symptoms of jaw bone problems during treatment with Lenvata®, including jaw pain, toothache, or sores on your gums. Tell your healthcare provider if you plan to have any dental procedures before or during treatment with Lenvata®. You should avoid having invasive dental procedures if possible, during treatment with Lenvata®. Stopping your bisphosphonate medicine before an invasive dental procedure may help decrease your risk of getting these jaw problems.
  - You should stop taking Lenvata® at least 1 week before planned dental surgery or invasive dental procedures.
  - Your healthcare provider should tell you when you may start taking Lenvata® again after dental procedures.

The most common side effects of Lenvata® in people treated for thyroid cancer include:
- tiredness
- decreased appetite
- mouth sores
- headache
- weight loss
- hoarseness
- joint and muscle pain
- stomach (abdomen) pain
- vomiting
- nausea
- rash, redness, itching, or peeling of your skin on your hands and feet

The most common side effects of Lenvata® when given with everolimus include:
- tiredness
- stomach (abdomen) pain
- vomiting
- weight loss
- swelling in your arms and legs
- cough
- decreased appetite
- rash
- mouth sores
- joint and muscle pain
- trouble breathing
- nausea
- bleeding

The most common side effects of Lenvata® in people treated for liver cancer include:
- tiredness
- weight loss
- change in thyroid hormone levels
- decreased appetite
- stomach (abdomen) pain
- bleeding
- joint and muscle pain
- hoarseness
- nausea
- rash, redness, itching, or peeling of your skin on your hands and feet

The most common side effects of Lenvata® when given with pembrolizumab include:
- decrease in thyroid hormone levels
- diarrhea
- decreased appetite
- stomach-area (abdomen) pain
- protein in your urine
- bleeding
- increased blood pressure
- joint and muscle pain
- vomiting
- weight loss
- constipation
- hoarseness
- tiredness
- nausea
- mouth sores
- urinary tract infection
- headache
- rash
- rash, redness, itching, or peeling of your skin on your hands and feet

Lenvata® may cause fertility problems in males and females. Talk to your healthcare provider if this is a concern for you.

Your healthcare provider may need to reduce your dose of Lenvata®, or delay or completely stop treatment, if you have certain side effects.

Call your healthcare provider right away if you have any of aforementioned symptoms.

Drug interactions
Lenvata® has been reported to prolong the QT/QTc interval. Avoid coadministration of Lenvata® with medicinal products with a known potential to prolong the QT/QTc interval.

Warnings
Before taking Lenvata®, tell your healthcare provider about all of your medical conditions, including if you:
- have high blood pressure
- have heart problems
- have a history of blood clots in your arteries (type of blood vessel), including stroke, heart attack, or change in vision
- have or have had liver or kidney problems
- have a history of a tear (perforation) in your stomach or intestine, or an abnormal connection between two or more body parts (fistula)
- have headaches, seizures, or vision problems
- have any bleeding problems
- plan to have surgery, a dental procedure, or have had a recent surgery. You should stop taking Lenvata® at least 1 week before planned surgery.
- are pregnant or plan to become pregnant. Lenvata® can harm your unborn baby.
- are breastfeeding or plan to breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Especially tell your healthcare provider if you are taking, or have taken, an osteoporosis medicine.

Missed dose
If you miss a dose of Lenvata®, take it as soon as you remember. If your next dose is due within 12 hours, skip the missed dose and take the next dose at your regular time.

Overdose
If you take too much Lenvata®, call your healthcare provider or go to the nearest hospital emergency room right away.

Pregnancy and lactation
Lenvata® can harm your unborn baby.
Females who are able to become pregnant:
- Your healthcare provider should do a pregnancy test before you start treatment with Lenvata®.
- You should use an effective method of birth control during treatment with Lenvata® and for 30 days after the last dose of Lenvata®. If you are using oral hormonal contraceptives, talk with your healthcare provider about adding another effective birth control method. Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with Lenvata®.

It is not known if Lenvata® passes into your breast milk. Do not breastfeed during treatment with Lenvata® and for at least 1 week after the last dose.

Patient information
- Take Lenvata® exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much Lenvata® to take and when to take it. Your healthcare provider may change your dose during treatment, stop treatment for some time, or completely stop treatment with Lenvata® if you have side effects.
- Take Lenvata® 1 time each day at the same time, with or without food.
- Use caution before driving or using machinery.
- Swallow Lenvata® capsules whole. Do not crush or chew the Lenvata® capsules.
- If you cannot swallow Lenvata® capsules whole, dissolve them. To dissolve them, pour a tablespoon of water or apple juice into a small glass and put the capsules into the liquid without breaking or crushing them. Leave for at least 10 minutes then stir for at least 3 minutes to dissolve the capsule shells. Drink the mixture. After drinking, add the same amount of water or apple juice, swirl and swallow.
- Caregivers should not open the capsules to avoid exposure to the contents of the capsule.

Storage
- Keep away from light and moisture. Store below 30°C.
- Keep out of the reach of children.
- Keep the desiccant in the bottle. Do not eat or throw away desiccant pack.
- Keep in the original container.
- Use appropriate precautions for handling and disposal of cytotoxic drugs.
- Safely throw away medicine that is out of date or no longer needed.

Packaging
Bottle of 30 Capsules

MANUFACTURED BY:
Noavaran Daroui Kimia Co., Tehran, Iran.
Telefax: +982166437014
www.kimia-pharma.co

References
https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/206947s024lbl.pdf
BNF 83 (British National Formulary) March 2022
https://www.ema.europa.eu/en/documents/product-information/lenvima-epar-product-information_en.pdf