LENVATA® CAPSULE

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LENVATA® 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 +982166435789 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 is from 1 to 4 hours.
Distribution: Mean steady state volume of distribution is 97 L. Protein binding is 97% to 99%.
Metabolism: The main metabolic pathways are enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes.
Excretion: Approximately 64% and 25% of the radiolabeled Lenvatinib 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 adult 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 anti-angiogenic 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) 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.

The safety and efficacy of Lenvata® have not been established in children.

Dosage and administration
The dosage of Lenvata® is determined by your healthcare provider, but the usual dosage of Lenvata® is as follows:
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:
  - o 20 mg orally once daily with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks.
  - o 18 mg orally once daily with everolimus 5 mg orally once daily.

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 blood pressure should be well controlled before you start taking Lenvata®. Your healthcare provider should check your blood pressure regularly 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:
  - o severe chest pain or pressure
  - o trouble talking
  - o pain in your arms, back, neck or jaw
  - o sudden severe headache
  - o shortness of breath
  - o numbness or weakness on one side of your body
  - o sudden vision changes
- **Liver problems.** Lenvata® may cause liver problems that may lead to liver failure and may 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 develop any of the following symptoms:
  - o your skin or the white part of your eyes turns yellow (jaundice)
  - o dark "tea colored" urine
  - o light-colored bowel movements (stools)
  - o 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. 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 develop 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 electrocardiogram (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 develop any signs or symptoms of bleeding during treatment with Lenvata®, including:
  - o red or black (looks like tar) stools
  - o blood in your urine
  - o severe and persistent nose bleeds
  - o coughing up blood or blood clots
  - o vomiting blood
  - o 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®. Tell your healthcare provider if you have symptoms such as tiredness, weight gain, constipation, feeling cold, dry skin or even rapid heart rate, sweating and weight loss.
- **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®.
  - o You should stop taking Lenvata® at least 1 week before planned surgery.
  - o Your healthcare provider should tell you when you may start taking Lenvata® again after surgery.
- **Severe jawbone problems (osteonecrosis).** Severe jawbone problems have happened in some people who take Lenvata®. 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 jawbone 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 jawbone 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.
  - o You should stop taking Lenvata® at least 1 week before planned dental surgery or invasive dental procedures.
  - o Your healthcare provider should tell you when you may start taking Lenvata® again after dental procedures.

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

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

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

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

The most common side effects of Lenvata® when given with pembrolizumab include:
- tiredness
- nausea
- vomiting
- joint and muscle pain
- decreased appetite
- weight loss
- constipation
- diarrhea
- headache
- stomach (abdomen) pain
- hoarseness
- feeling dizzy
- back pain
- swelling of the legs
- high or low blood pressure
- hair loss
- indigestion
- trouble sleeping
- loss of body fluids
- increase in amylase or lipase
- thickening of the skin
- feeling unwell
- heart palpitations
- feeling bloated
- inflammation of the colon (colitis)
- blood clots in the lungs (difficulty breathing, chest pain)
- inflammation of the pancreas or gallbladder
- kidney failure (e.g., renal tubular necrosis)
- a hole (perforation) in the stomach or intestines
- decrease or increase in thyroid hormone levels
- decreased secretion of hormones produced by adrenal glands
- low levels of platelets in the blood (bruising and difficult wound healing)
- decrease in the number of white blood cells or red blood cells
- changes in blood test results for calcium or potassium or magnesium levels (low)
- changes in blood test results for cholesterol levels (high)
- dry, sore, or inflamed mouth, odd taste sensation
- bleeding (nose bleeds, blood in the urine, bruising, bleeding from the gums or gut wall)
- changes in blood test results for liver or kidney function
- rash, redness, itching, soreness, swelling, or peeling of your skin on your hands and feet (palmar-plantar erythrodysesthesia)
- changes in urine tests for protein (high) and urinary infections (increased frequency in urination and pain in passing urine)

Other most common side effects of Lenvata® include:
- cerebrovascular insufficiency
- hepatic coma or other disorders
- encephalopathy
- increase of bilirubin in blood
- decrease of albumin in blood
- increased risk of infection

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

Drug interactions
Since the drug interactions with Lenvata® are not limited to the following medicines tell your healthcare provider or pharmacist if you are taking, have recently taken or might take any other medicines. This includes herbal medicines and other medicines you bought without a prescription.
Tell your healthcare provider before taking Lenvata® if you are taking any of the following medicines.
- Ketoconazole - to treat fungal infections
- Rifampicin - to treat tuberculosis
- 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 or have had liver or kidney problems
- have heart problems
- have any bleeding problems
- have headaches, seizures, or vision problems
- are over 75 years
- have had recent radiotherapy
- are breastfeeding or plan to breastfeed.
- weigh less than 60 kg
- are pregnant or plan to become pregnant.
- have a history of blood clots in your arteries (type of blood vessel), including stroke, heart attack, or change in vision
- have a history of a tear (perforation) in your stomach or intestine, or an abnormal connection between two or more body parts (fistula)
- 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.
- If you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.

Tell your healthcare provider about all the medicines you take or treatments you receive, 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 or cancer medicines which alter formation of blood vessels (so called angiogenesis inhibitors). You should not start or stop any medicine before you talk with the healthcare provider that prescribed Lenvata®. Lenvata® and other medicines may affect each other causing serious side effects.

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:**
  - o Your healthcare provider should do a pregnancy test before you start treatment with Lenvata®.
  - o You should use an effective method of birth control (contraception) during treatment with Lenvata® and for at least 30 days after the last dose of Lenvata®.
  - o Because it is not known if Lenvata® can reduce the effect of the oral contraceptive pill, if this is your normal method of contraception you should ensure you also add a barrier method such as the cap or condoms if you have sex during treatment with Lenvata®. Talk with your healthcare provider about birth control methods you can use during this time.
  - o Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with Lenvata®.
- Lenvata® may cause fertility problems in males and females. Talk to your healthcare provider if this is a concern for you.
- It is not known if Lenvata® passes into your breast milk. Do not breastfeed during treatment with Lenvata® and for 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.
- Swallow Lenvata® capsules whole. Do not crush or chew the Lenvata® capsules.
- Do not open the capsules to avoid exposure to the contents of the capsule.
- If you cannot swallow Lenvata® capsules whole, Lenvata® capsules can be mixed with water or apple juice, then taken by mouth, or mixed with water and given through a feeding tube.
- **How to take Lenvata® by mouth if you cannot swallow whole capsules:**
  - o Place your daily dose, up to 5 capsules, in a small container or oral syringe (approximately 20 mL capacity).
  - o Add 3 mL of **water or apple juice** to the container or oral syringe. **Wait 10 minutes** for the capsule shell (outer surface) to dissolve completely, then stir or shake the mixture for 3 minutes until capsules are fully dissolved. Do not break or crush the capsules.
  - o Drink the liquid mixture or use an oral syringe to take directly into the mouth.
  - o Next, using a second syringe, add an additional 2 mL of liquid to the container or oral syringe (cap the first oral syringe before adding the additional water) then swirl or shake and take the liquid mixture. Repeat this step at least one time and until you cannot see any of the Lenvata® mixture left in the container or oral syringe to make sure all of the medicine is taken.
  - o If 6 capsules are required for your daily dose, follow the above instructions using 3 capsules at a time.
- **How to give Lenvata® through a feeding tube:**
  - o Lenvata® should be given in feeding tubes of at least 5 French diameter (polyvinyl chloride or polyurethane tube) and at least 6 French diameter (silicone tube).
  - o Place your daily dose, up to 5 capsules, in a syringe (20 mL capacity).
  - o Add 3 mL of **water** to the syringe. **Wait 10 minutes** for the capsule shell (outer surface) to dissolve completely, then stir or shake the mixture for 3 minutes until capsules are fully dissolved. Do not break or crush the capsules.
  - o Give the mixture through a feeding tube.
  - o Next, cap the syringe and remove the plunger. Use a second syringe and add an additional 2 mL of liquid to the syringe. Swirl or shake and give the mixture in the feeding tube. Repeat this step at least one time and until you cannot see any of the Lenvata® mixture left in the syringe to make sure all of the medicine is taken.
  - o If 6 capsules are required for your daily dose, follow the above instructions using 3 capsules at a time.
- Lenvata® mixture may be stored in a covered container in the refrigerator at 2°C to 8°C (36°F to 46°F) for a maximum of 24 hours. Throw away the Lenvata® mixture if not used within 24 hours of mixing.
- Lenvata® may cause side effects that can affect your ability to drive or use machines. Avoid driving or using machines if you feel dizzy or tired.

Storage
- Keep away from light and moisture. Store below 30°C.
- Keep out of the reach of children.
- Keep in the original container.
- Keep the desiccant in the bottle. Do not eat or throw away the desiccant pack.
- Safely throw away medicine that is out of date or that you no longer need. Ask your pharmacist how to safely throw away Lenvata® capsules.
- Use appropriate precautions for handling and disposal of cytotoxic drugs.

Packaging
Bottle of 30 Capsules.

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MANUFACTURED BY: Noavaran Daroui Kimia Co., Tehran, Iran.
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References
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