Package leaflet: Information for the user

Lenvatinib Accord 4 mg hard capsules
Lenvatinib Accord 10 mg hard capsules

lenvatinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1 What Lenvatinib Accord is and what it is used for

Lenvatinib Accord is a medicine that contains the active substance lenvatinib. It is used on its own to treat progressive or advanced thyroid cancer in adults when radioactive iodine treatment has not helped to stop the disease.

Lenvatinib Accord can also be used on its own to treat liver cancer (*hepatocellular carcinoma*) in adults who have not previously been treated with another anticancer medicine that travels through the bloodstream. People get Lenvatinib Accord when their liver cancer has spread or cannot be taken out by surgery.

Lenvatinib Accord can also be used together with another anticancer medicine called pembrolizumab to treat advanced cancer of the lining of the uterus (*endometrial carcinoma*) in adults whose cancer has spread after being previously treated with another anticancer medicine that travels through the bloodstream and cannot be taken out by surgery or radiation treatment.

How Lenvatinib Accord works
Lenvatinib Accord blocks the action of proteins called receptor tyrosine kinases (RTKs), which are involved in the development of new blood vessels that supply oxygen and nutrients to cells and help them to grow. These proteins can be present in high amounts in cancer cells, and by blocking their action Lenvatinib Accord may slow the rate at which the cancer cells multiply and the tumour grows and help to cut off the blood supply that the cancer needs.

2 What you need to know before you take Lenvatinib Accord

Do not take Lenvatinib Accord if:
- you are allergic to lenvatinib or any of the other ingredients of this medicine (listed in section 6).
- you are breast-feeding (see the section below on Contraception, pregnancy and breast-feeding).

Warnings and precautions

Talk to your doctor before taking Lenvatinib Accord if you:
- have high blood pressure
- are a woman able to become pregnant (see the section below on Pregnancy, breast-feeding and fertility)
- have a history of heart problems or stroke
- have liver or kidney problems
- have had recent surgery or radiotherapy
- need to have a surgical procedure. Your doctor may consider stopping Lenvatinib Accord if you will be undergoing a major surgical procedure as Lenvatinib Accord may affect wound healing. Lenvatinib Accord may be restarted once adequate wound healing is established.
- are over 75 years
- belong to an ethnic group other than White or Asian
- weigh less than 60 kg
- have a history of abnormal connections (known as a fistula) between different organs in the body or from an organ to the skin
- If you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.
- have or have had pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. You may be advised to have a dental check-up before starting Lenvatinib Accord as bone damage in the jaw (osteonecrosis) has been reported in patients treated with Lenvatinib Accord. If you need to undergo an invasive dental treatment or dental surgery, tell your dentist that you are being treated with Lenvatinib Accord, particularly when you are also receiving or have received injections of bisphosphonates (used to treat or prevent bone disorders).
- are receiving or have received some medicines used to treat osteoporosis (antiresorptive medicines) or cancer medicines which alter formation of blood vessels (so called angiogenesis inhibitors), as the risk of bone damage in the jaw may be increased.

Before taking Lenvatinib Accord, your doctor may carry out some tests, for example to check your blood pressure and your liver or kidney function and to see if you have low levels of salt and high levels of thyroid stimulating hormone in your blood. Your doctor will discuss the results of these tests with you and decide whether you can be given Lenvatinib Accord. You may need to have additional treatment with other medicines, to take a lower dose of Lenvatinib Accord, or to take extra care due to an increased risk of side effects.

If you are not sure talk to your doctor before taking Lenvatinib Accord.

Conditions you need to look out for
During treatment of your cancer, the breakdown of tumour cells may leak substances into the blood which may lead to a group of complications called tumour lysis syndrome (TLS). This may lead to changes in your kidneys and can be life-threatening. Your doctor will observe and may give you a treatment to reduce the risk. Tell your doctor immediately if you experience signs of TLS (see section 4: Possible side effects).

Children and adolescents
Lenvatinib Accord is not currently recommended for use in children and adolescents younger than 18 years old.

Other medicines and Lenvatinib Accord
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes herbal preparations and medicines without a prescription.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- If you could become pregnant, use highly effective contraception while taking this medicine, and for at least one month after you finish treatment. Because it is not known if Lenvatinib Accord 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 Lenvatinib Accord.
- Do not take Lenvatinib Accord if you are planning to become pregnant during your treatment. This is because it may seriously harm your baby.
- If you become pregnant while being treated with Lenvatinib Accord, tell your doctor immediately. Your doctor will help you decide whether the treatment should be continued.
- Do not breast-feed if you are taking Lenvatinib Accord. This is because the medicine passes into breast milk and may seriously harm your breastfed baby.

Driving and using machines
Lenvatinib Accord 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.

Lenvatinib Accord contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially 'sodium-free'.

3 How to take Lenvatinib Accord

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
Thyroid cancer
- The recommended dose of Lenvatinib Accord is usually 24 mg once a day (2 capsules of 10 mg and 1 capsule of 4 mg).
- If you have severe liver or kidney problems the recommended dose is 14 mg once a day (1 capsule of 10 mg and 1 capsule of 4 mg).
- Your doctor may reduce your dose if you have problems with side effects.

Liver cancer
- The recommended dose of Lenvatinib Accord depends on your body weight when you first start treatment. The dose is usually 12 mg once a day (3 capsules of 4 mg) if you weigh 60 kg or more and 8 mg once a day (2 capsules of 4 mg) if you weigh less than 60 kg.
- Your doctor may reduce your dose if you have problems with side effects.

Uterine cancer
- The recommended dose of Lenvatinib Accord is 20 mg once a day (2 capsules of 10 mg), in combination with pembrolizumab. The pembrolizumab is given by your doctor as an injection in your vein, either 200 mg every 3 weeks or 400 mg every 6 weeks.
- Your doctor may reduce your dose if you have problems with side effects.

Taking this medicine
- You can take the capsules with or without food.
- Do not open the capsules to avoid exposure to the contents of the capsule.
- Swallow the capsules whole with water. If you cannot swallow the capsules whole, a liquid mixture can be prepared using water, apple juice, or milk. The liquid mixture may be given by mouth or through a feeding tube. If given through a feeding tube, then the liquid mixture should be prepared using water. If not used at the time of preparation, the liquid mixture may be stored in a covered container and must be refrigerated at 2ºC to 8ºC for a maximum of 24 hours. Shake the liquid mixture for 30 seconds after removing from the refrigerator. If the liquid mixture is not used within 24 hours of preparation, it should be thrown away.
- Preparation and administration of the liquid mixture:

  - Place the whole capsule(s) corresponding to the prescribed dose (up to 5 capsules) in a small container (approximately 20 mL (4 tsp) capacity) or oral syringe (20 mL); do not break or crush capsules.
  - Add 3 mL of liquid to the container or oral syringe. Wait 10 minutes for the capsule shell (outer surface) to dissolve, then stir or shake the mixture for 3 minutes until the capsules are fully dissolved.
    - If liquid mixture is prepared in an oral syringe, cap the syringe, remove plunger and use a second syringe or medicine dropper to add the liquid to the first syringe, then replace plunger prior to mixing.
  - Drink the liquid mixture from the container or use an oral syringe to take directly into the mouth or through a feeding tube.
- Next, add an additional 2 mL of liquid to the container, or oral syringe using a second syringe or dropper, swirl or shake and take the liquid mixture. Repeat this step at least twice and until there is no visible sign of the mixture to make sure all of the medication is taken.
- Take the capsules at about the same time each day.

How long to take Lenvatinib Accord
You will usually carry on taking this medicine as long as you are getting benefit.

If you take more Lenvatinib Accord than you should
If you take more Lenvatinib Accord than you should, talk to a doctor or pharmacist straight away. Take the medicine pack with you.

If you forget to take Lenvatinib Accord
Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

What to do if you forget to take your dose depends on how long it is until your next dose.
- If it is 12 hours or more until your next dose: take the missed dose as soon as you remember. Then take the next dose at the normal time.
- If it is less than 12 hours until your next dose: skip the missed dose. Then take the next dose at the normal time.

4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor straight away if you notice any of the following side effects - you may need urgent medical treatment:
- feeling numb or weak on one side of your body, severe headache, seizure, confusion, difficulty talking, vision changes or feeling dizzy - these may be signs of a stroke, bleeding in your brain, or the effect on your brain of a severe increase in blood pressure.
- chest pain or pressure, pain in your arms, back, neck or jaw, being short of breath, rapid or irregular heart rate, coughing, bluish colour to lips or fingers, feeling very tired – these may be signs of a heart problem, a blood clot in your lung or a leak of air from your lung into your chest so your lung cannot inflate.
- severe pain in your belly (abdomen) - this may be due to a hole in the wall of your gut or a fistula (a hole in your gut which links through a tube-like passage to another part of your body or skin).
- black, tarry, or bloody stools, or coughing up of blood - these may be signs of bleeding inside your body.
- yellow skin or yellowing of the whites of the eyes (jaundice) or drowsiness, confusion, poor concentration – these may be signs of liver problems.
- diarrhoea, feeling and being sick (nausea and vomiting) - these are very common side effects that can become serious if they cause you to become dehydrated, which can lead to kidney failure. Your doctor can give you medicine to reduce these side effects.

- pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth - these could be signs of bone damage in the jaw (osteonecrosis).
- nausea, shortness of breath, irregular heartbeat, muscular cramps, seizure, clouding of urine and tiredness. These symptoms may be complications due to the breakdown products of dying cancer cells and known as tumour lysis syndrome (TLS).

Tell your doctor straight away if you notice any of the side effects above.

The following side effects may happen with this medicine when given alone:

Very common (may affect more than 1 in 10 people)
- high or low blood pressure
- loss of appetite or weight loss
- feeling sick (nausea) and being sick (vomiting), constipation, diarrhoea, abdominal pain, indigestion
- feeling very tired or weak
- hoarse voice
- swelling of the legs
- rash
- dry, sore, or inflamed mouth, odd taste sensation
- joint or muscle pain
- feeling dizzy
- hair loss
- bleeding (most commonly nose bleeds, but also other types of bleeding such as blood in the urine, bruising, bleeding from the gums or gut wall)
- trouble sleeping
- changes in urine tests for protein (high) and urinary infections (increased frequency in urination and pain in passing urine)
- headache
- back pain
- redness, soreness and swelling of the skin on the hands and feet (palmar-plantar erythrodysaesthesia)
- underactive thyroid (tiredness, weight gain, constipation, feeling cold, dry skin)
- changes in blood test results for potassium levels (low) and calcium levels (low)
- decrease in the number of white blood cells
- changes in blood test results for liver function
- low levels of platelets in the blood which may lead to bruising and difficulty in wound healing
- changes in blood test results for magnesium (low), cholesterol (high) and thyroid stimulating hormone (high)
- changes in blood test results for kidney function and kidney failure
- increase in lipase and amylase (enzymes involved in digestion)

Common (may affect up to 1 in 10 people)
- loss of body fluids (dehydration)
- heart palpitations
- dry skin, thickening and itching of the skin
- feeling bloated or having excess wind
- heart problems or blood clots in the lungs (difficulty breathing, chest pain) or other organs
- liver failure
- drowsiness, confusion, poor concentration, loss of consciousness that may be signs of liver failure
- feeling unwell
- inflammation of the gallbladder
- stroke
- anal fistula (a small channel that forms between the anus and the surrounding skin)
- a hole (perforation) in the stomach or intestines

Uncommon (may affect up to 1 in 100 people)
- painful infection or irritation near the anus
- mini-stroke
- liver damage
- severe pain in the upper left part of the belly (abdomen) which may be associated with fever, chills, nausea and vomiting (splenic infarction)
- inflammation of the pancreas
- wound healing problems
- bone damage in the jaw (osteonecrosis)
- inflammation of the colon (colitis)
- decreased secretion of hormones produced by adrenal glands

Rare (may affect up to 1 in 1,000 people)
- Tumour lysis syndrome (TLS)

Not known (frequency cannot be estimated from the available data)
- other types of fistulae (an abnormal connection between different organs in the body or between the skin and an underlying structure such as throat and windpipe). Symptoms depend on where the fistula is located. Talk to your doctor if you experience any new or unsual symptoms such as coughing when swallowing.
- an enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections).

The following side effects may happen with this medicine when given in combination with pembrolizumab:

Very common (may affect more than 1 in 10 people)
- changes in urine tests for protein (high) and urinary infections (increased frequency in urination and pain in passing urine)
- low levels of platelets in the blood which may lead to bruising and difficulty in wound healing
- decrease in the number of white blood cells
- decrease in the number of red blood cells
- underactive thyroid (tiredness, weight gain, constipation, feeling cold, dry skin) and changes in blood test results for thyroid stimulating hormone (high)
- overactive thyroid (symptoms can include rapid heart rate, sweating and weight loss)
- changes in blood test results for calcium levels (low)
- changes in blood test results for potassium levels (low)
- changes in blood test results for cholesterol levels (high)
- changes in blood test results for magnesium levels (low)
- loss of appetite or weight loss
- feeling dizzy
- headache
- back pain
- dry, sore, or inflamed mouth, odd taste sensation
- bleeding (most commonly nose bleeds, but also other types of bleeding such as blood in the urine, bruising, bleeding from the gums or gut wall)
- high blood pressure
- hoarse voice
- feeling sick (nausea) and being sick (vomiting), constipation, diarrhoea, abdominal pain
- increase in amylase (enzyme involved in digestion)
- increase in lipase (enzyme involved in digestion)
- changes in blood test results for liver function
- changes in blood test results for kidney function

– redness, soreness and swelling of the skin on the hands and feet (palmar-plantar erythrodysaesthesia)
– rash
– joint or muscle pain
– feeling very tired or weak
– swelling of the legs

Common (may affect up to 1 in 10 people)
– loss of body fluids (dehydration)
– trouble sleeping
– heart palpitations
– low blood pressure
– blood clots in the lungs (difficulty breathing, chest pain)
– inflammation of the pancreas
– feeling bloated or having excess wind
– indigestion
– inflammation of the gallbladder
– hair loss
– kidney failure
– feeling unwell
– inflammation of the colon (colitis)
– decreased secretion of hormones produced by adrenal glands
– a hole (perforation) in the stomach or intestines

Uncommon (may affect up to 1 in 100 people)
– headache, feeling confused, seizure, and changes in vision
– signs of a stroke, including feeling numb or weak on one side of your body, severe headache, seizure, confusion, difficulty talking, vision changes or feeling dizzy
– mini-stroke
– signs of a heart problem, including chest pain or pressure, pain in your arms, back, neck or jaw, being short of breath, rapid or irregular heart rate, coughing, bluish colour to lips or fingers, and feeling very tired
– severe difficulty breathing and chest pain, caused by a leak of air from your lung into your chest so your lung cannot inflate
– painful infection or irritation near the anus
– anal fistula (a small channel that forms between the anus and the surrounding skin)
– liver failure or signs of liver damage, including yellow skin or yellowing of the whites of the eyes (jaundice) or drowsiness, confusion, poor concentration
– dry skin, thickening and itching of the skin
– wound healing problems

Rare (may affect up to 1 in 1,000 people)
– Tumour lysis syndrome (TLS)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via
HPRA Pharmacovigilance
Website: www.hpra.ie.
By reporting side effects you can help provide more information on the safety of this medicine.

5 How to store Lenvatinib Accord

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after 'EXP'. The expiry date refers to the last day of that month.

Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6 Contents of the pack and other information

What Lenvatinib Accord contains
- The active substance is lenvatinib.
  - Lenvatinib Accord 4 mg hard capsules: - Each hard capsule contains lenvatinib besilate equivalent to 4 mg lenvatinib.
  - Lenvatinib Accord 10 mg hard capsules: - Each hard capsule contains lenvatinib besilate equivalent to 10 mg lenvatinib.
- The other ingredients are sodium hydrogen carbonate, mannitol, microcrystalline cellulose, hydroxypropylcellulose, low-substituted hydroxypropylcellulose, talc.
- The capsule shell of the 4 mg capsules contains hypromellose, titanium dioxide, iron oxide yellow (E172), iron oxide red (E172), iron oxide black (E172).
- The capsule shell of the 10 mg capsules contains hypromellose, titanium dioxide, iron oxide yellow (E172)
- The capsule cap contains hypromellose, titanium dioxide, iron oxide yellow (E172), iron oxide red (E172), iron oxide black (E172).
- The printing ink contains shellac, iron oxide black (E172), potassium hydroxide.

What Lenvatinib Accord looks like and contents of the pack
- The 4 mg hard capsule (capsule) is a caramel opaque body and caramel opaque cap (approximately 14.3 mm in length), printed with "L7VB" over "4".
- The 10 mg hard capsule (capsule) is a yellow opaque body and caramel opaque cap (approximately 14.3 mm in length), printed with "L7VB" over "10".
- Each carton contains 30, 60 or 90 hard capsules in oPA/Al/PVC/Al blisters or 30x1, 60x1 or 90x1 hard capsules in oPA/Al/PVC/Al unit dose blisters.
- Each carton contains 30, 60 or 90 hard capsules in oPA/Al/PVC/PE/Al blisters with desiccant or 30x1, 60x1 or 90x1 hard capsules in oPA/Al/PVC/PE/Al unit dose blisters with desiccant.

Not all pack sizes may be marketed.

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Accord Healthcare Ireland Ltd
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This medicine is authorised in the Member States of the European Economic Area under the following names:

Netherlands	Lenvatinib Accord 4 mg, harde capsules; Lenvatinib Accord 10 mg, harde capsules
Austria	Lenvatinib Accord 4 mg Hartkapseln; Lenvatinib Accord 10 mg Hartkapseln
Belgium	Lenvatinib Accord 4 mg gélules; Lenvatinib Accord 10 mg gélules
Czech	Lenvatinib Accord
Denmark	Lenvatinib Accord
Finland	Lenvatinibia Accord 4 mg kapseli, kova; Lenvatinibia Accord 10 mg kapseli, kova
France	Lenvatinib Accord 4 mg, gélule; Lenvatinib Accord 10 mg, gélule
Germany	Lenvatinib Accord 4 mg Hartkapseln; Lenvatinib Accord 10 mg Hartkapseln
Hungary	Lenvatinib Accord 4 mg kemény kapszula; Lenvatinib Accord 10 mg kemény kapszula
Italy	Lenvatinib Accord
Norway	Lenvatinib Accord
Portugal	Lenvatinib Accord
Spain	Lenvatinib Accord 4 mg cápsulas duras EFG; Lenvatinib Accord 10 mg cápsulas duras EFG
Sweeden	Lenvatinib Accord 4 mg; Lenvatinib Accord 10 mg

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