Package leaflet: Information for the patient

Vargatef® 100 mg soft capsules
nintedanib

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 or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vargatef is and what it is used for

Vargatef capsules contain the active substance nintedanib. Nintedanib blocks the activity of a group of proteins which are involved in the development of new blood vessels that cancer cells need to supply them with food and oxygen. By blocking the activity of these proteins, nintedanib can help stop the growth and spread of the cancer.

This medicine is used in combination with another cancer medicine (docetaxel) to treat a cancer of the lung called non-small cell lung cancer (NSCLC). It is for adult patients whose NSCLC is of a certain type ("*adenocarcinoma*") and who had already received one treatment with another medicine to treat this cancer but whose tumour started to grow again.

2. What you need to know before you take Vargatef

Do not take Vargatef
- if you are allergic to nintedanib, to peanut or soya, or to any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions
Talk to your doctor or pharmacist before taking this medicine
- if you have or had liver problems, if you have or had bleeding problems, particularly recent bleeding in the lung
- if you have or have had problems with your kidneys or if an increased amount of protein has been detected in your urine
- if you take blood-thinning medicines (such as warfarin, phenprocoumon, heparin or acetylsalicylic acid) to prevent blood clotting. Treatment with Vargatef may lead to a higher risk of bleeding
- if you have recently had a surgery or plan to have a surgery. Nintedanib may affect the way your wounds heal. Therefore treatment with Vargatef will usually be interrupted if you are having surgery. Your doctor will decide when to resume your treatment with this medicine

- if you have cancer that has spread to the brain
- if you have high blood pressure
- if you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall

Based on this information your doctor may carry out some blood tests, for example to check your liver function and to determine how fast your blood can clot. Your doctor will discuss the results of these tests with you and decide whether you can be given Vargatef.

Inform your doctor immediately while taking this medicine
- if you get diarrhoea. Treatment of diarrhoea at the first signs is important (see section 4)
- if you vomit or feel sick (nausea)
- if you have unexplained symptoms such as yellowing of your skin or the white part of your eyes (jaundice), dark or brown (tea coloured) urine, pain on the upper right side of your stomach area (abdomen), bleeding or bruising more easily than normal, or feeling tired. This could be symptoms of serious liver problems
- if you develop fever, chills, fast breathing or a fast heartbeat. These could be signs of infection or infection of the blood (sepsis) (see section 4)
- if you experience severe pain in your stomach area, fever, chills, sickness, vomiting, or abdominal rigidity or bloating, as these could be symptoms of a hole in the wall of your gut (‘gastrointestinal perforation’)
- if you experience a combination of some or all of the symptoms thereafter: sudden severe abdominal pain or cramping, red blood in your stool, diarrhoea or constipation, nausea and vomiting as these could be symptoms of a bowel inflammation from reduced blood flow (‘ischaemic colitis’)
- if you experience pain, swelling, reddening, warmth of a limb or if you experience chest pain and difficulty to breathe as these could be symptoms of a blood clot in one of your veins
- if you have any major bleeding
- if you experience chest pressure or pain, typically on the left side of the body, pain in the neck, jaw, shoulder or arm, a fast heartbeat, shortness of breath, nausea, vomiting, as this could be symptoms of a heart attack
- if you experience symptoms such as headache, vision changes, confusion, seizure or other neurologic disturbances such as weakness in an arm or a leg, with or without high blood pressure. This could be symptoms of a brain condition called posterior reversible encephalopathy syndrome (PRES)
- if any side effect(s) you may get (see section 4) becomes serious

Children and adolescents
This medicine has not been studied in children or adolescents to treat a cancer of the lung (NSCLC) and is therefore not to be taken by children and adolescents below the age of 18 years.

Other medicines and Vargatef
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including herbal medicines and medicines obtained without a prescription.

This medicine can interact with certain other medicines. The following medicines may increase the blood levels of nintedanib, the active substance of Vargatef, and hence may increase the risk for side effects (see section 4):
- Ketoconazole (used to treat fungal infections)
- Erythromycin (used to treat bacterial infections)

The following medicines may decrease the blood levels of nintedanib and thus may lead to reduction of the effectiveness of Vargatef:
- Rifampicin (an antibiotic used to treat tuberculosis)
- Carbamazepine, phenytoin (used to treat seizures)
- St. John’s Wort (a herbal medicine to treat depression)

Pregnancy and breast-feeding
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.

Pregnancy
Do not take this medicine during pregnancy, as it can harm your unborn baby and cause birth defects.

Contraception
- Women who can become pregnant must use a highly effective method of birth control to prevent pregnancy, when they start taking Vargatef, while they are taking Vargatef and for at least 3 months after stopping treatment.
- You should discuss the most appropriate methods of contraception for you with your doctor.
- Vomiting and/or diarrhoea or other gastrointestinal conditions can affect the absorption of oral hormonal contraceptives, such as birth control pills, and may reduce their effectiveness. Therefore, if experiencing these, talk to your doctor to discuss an alternative more appropriate method of contraception.
- Tell your doctor or pharmacist immediately if you become pregnant or think you may be pregnant during treatment with Vargatef.

Breast-feeding
It is not known if the medicine passes into breast milk and could cause harm to a breast-fed child. Therefore, women should not breast-feed during treatment with Vargatef.

Fertility
The effect of this medicine on human fertility has not been investigated.

Driving and using machines
Vargatef may have minor influence on your ability to drive and use machines. You should not drive or use machines if you feel sick.

Vargatef contains soya
The capsules contain soya lecithin. If you are allergic to peanut or soya, do not use this medicine.

3. How to take Vargatef

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

Do not take Vargatef on the same day as your chemotherapy treatment with docetaxel.

Swallow the capsules whole with water and do not chew them. It is recommended to take the capsules with food, i.e. during or immediately before or after a meal.
Do not open or crush the capsule (see section 5).

The recommended dose is four capsules per day (this is a total of 400 mg nintedanib per day). Do not take more than this dose.

This daily dose should be split into two doses of two capsules about 12 hours apart, for example two capsules in the morning and two capsules in the evening. These two doses should be taken at around the same time each day. Taking the medicine this way ensures that a steady amount of nintedanib is maintained in the body.

Dose reduction
If you cannot tolerate the recommended dose of 400 mg per day because of side effects (see section 4), your doctor may reduce the daily dose of Vargatef. Do not reduce the dose or stop the treatment yourself without consulting your doctor first.

Your doctor may reduce your recommended dose to 300 mg per day (two capsules of 150 mg). In this case your doctor will prescribe Vargatef 150 mg soft capsules for your treatment.

If necessary, your doctor may further reduce your daily dose to 200 mg per day (two capsules of 100 mg). You will be prescribed the appropriate capsule strength by your doctor if this happens.

In both cases, you should take one capsule of the appropriate strength twice daily approximately 12 hours apart with food (for example in the morning and in the evening) at about the same time of the day.

In case your doctor has stopped your chemotherapy with docetaxel you should continue to take Vargatef twice daily.

If you take more Vargatef than you should
Contact your doctor or pharmacist immediately.

If you forget to take Vargatef
Do not take a double dose to make up for a forgotten dose. Take your next dose of Vargatef as planned at the next scheduled time and at the dose recommended by your doctor or pharmacist.

If you stop taking Vargatef
Do not stop taking Vargatef without consulting your doctor first. It is important to take this medicine every day, as long as your doctor prescribes it for you. If you do not take this medicine as prescribed by your doctor, this cancer treatment may not work properly.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

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

You need to pay special attention if you get the following side effects during treatment with Vargatef:

- ***Diarrhoea*** *(very common, may affect more than 1 in 10 people)*

Diarrhoea may lead to a loss of fluid and important salts (electrolytes, such as sodium or potassium) in your body. At the first signs of diarrhoea drink plenty of fluids and contact your doctor immediately. Start appropriate anti-diarrhoeal treatment, e.g. with loperamide, as soon as possible after having contacted your doctor.

- ***Febrile neutropenia*** *and* ***sepsis*** *(common, may affect up to 1 in 10 people)*

Treatment with Vargatef may lead to a reduced number of a type of your white blood cells (*neutropenia*) which are important for the body's reaction against bacterial or fungal infections. As a consequence of neutropenia, fever (*febrile neutropenia*) and blood infection (*sepsis*) may occur. Tell your doctor immediately if you develop fever, chills, fast breathing or a fast heartbeat.
During treatment with Vargatef your doctor will regularly monitor your blood cells and examine you for signs of infection, such as inflammation, fever or tiredness.

The following side effects were observed under treatment with this medicine:

Very common side effects (may affect more than 1 in 10 people)
- Diarrhoea – please see above
- Painful, numb and/or tingling feeling in fingers and toes (*peripheral neuropathy*)
- Feeling sick (*nausea*)
- Throwing up (*vomiting*)
- Pain in the stomach (abdomen)
- Bleeding
- Decrease in the number of white blood cells (*neutropenia*)
- Inflammation of the mucous membranes lining the digestive tract including sores and ulcers in the mouth (*mucositis, including stomatitis*)
- Rash
- Decreased appetite
- Electrolyte imbalance
- Increased liver enzyme values (alanine aminotransferase, aspartate aminotransferase, blood alkaline phosphatase) in the blood as seen from blood tests
- Hair loss (alopecia)

Common side effects (may affect up to 1 in 10 people)
- Blood poisoning (*sepsis*) - please see above
- Decrease in the number of white blood cells accompanied by fever (*febrile neutropenia*)
- Blood clots in the veins (*venous thromboembolism*), especially in the legs (symptoms include pain, redness, swelling, and warmth of a limb), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing (if you notice any of these symptoms, seek medical advice immediately)
- High blood pressure (*hypertension*)
- Fluid loss (*dehydration*)
- Abscesses
- Low platelet count (*thrombocytopenia*)
- Jaundice (*hyperbilirubinaemia*)
- Increased liver enzyme values (gamma-glutamyltransferase) in the blood as seen from blood tests
- Weight loss
- Itching
- Headache
- Increased amount of protein in your urine (*proteinuria*)

Uncommon side effects (may affect up to 1 in 100 people)
- Occurrence of holes in the wall of your gut (*gastrointestinal perforation*)
- Serious liver problems
- Inflammation of the pancreas (*pancreatitis*)
- Myocardial infarction
- Renal failure

Not known (cannot be estimated from the available data)
- Inflammation of the large bowel
- An enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections)
- A brain condition with symptoms such as headache, vision changes, confusion, seizure or other neurologic disturbances such as weakness in an arm or a leg, with or without high blood pressure (posterior reversible encephalopathy syndrome)

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 (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

5. How to store Vargatef

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, wrapper and blisters. The expiry date refers to the last day of that month.

Do not store above 25°C.
Store in the original package in order to protect from moisture.

Do not use this medicine if you notice that the blister containing the capsules is opened or a capsule is broken.
If you are in contact with the content of the capsule, wash off your hands immediately with plenty of water (see section 3).

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 Vargatef contains
The active substance is nintedanib. Each soft capsule contains 100 mg nintedanib (as esilate).

The excipients are:

Capsule content:	Triglycerides medium-chain, hard fat, soya lecithin (E322)
Capsule shell:	Gelatin, glycerol (85 %), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172)
Printing ink:	Shellac, iron oxide black (E172), propylene glycol (E1520)

What Vargatef looks like and contents of the pack
Vargatef 100 mg soft capsules (capsules) are peach-coloured, opaque, oblong capsules imprinted on one side in black with the Boehringer Ingelheim company symbol and the figure “100”.

Three pack-sizes of Vargatef 100 mg soft capsules are available:
- One box containing 60 capsules (6 aluminium blisters of 10 capsules each).
- One box containing 120 capsules (12 aluminium blisters of 10 capsules each).
- A multipack containing 120 capsules (2 boxes of 60 capsules each, bundled together by a wrapping foil).

Not all pack sizes of Vargatef 100 mg soft capsules may be marketed.

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Additional Information:
Boehringer Ingelheim logo