Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a physician's prescription only

Vargatef®

100 mg

Soft capsules

Each capsule of Vargatef 100 mg contains

nintedanib 100 mg (as esilate)

Vargatef®

150 mg

Soft capsules

Each capsule of Vargatef 150 mg contains

nintedanib 150 mg (as esilate)

For the list of inactive ingredients – see section 2 under 'Important information about some of the medicine's ingredients' and section 6 'Additional information'.

Read the entire leaflet carefully before using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, refer to the physician or the pharmacist.

This medicine has been prescribed to treat your medical condition. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar.

1. What is this medicine intended for?

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

This medicine is used in combination with the chemotherapy medicine docetaxel to treat adults with locally advanced, metastatic or recurrent cancer of the lung called non-small cell lung cancer (abbreviated as NSCLC) classified as adenocarcinoma, following tumor recurrence despite having received previous treatment for their disease.

Therapeutic group: anti-neoplastic agents, kinase inhibitors.

2. Before using this medicine

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient nintedanib, to peanuts or soy, or to any of the other ingredients that this medicine contains (see section 6 in this leaflet).

Special warnings regarding the use of this medicine
Consult your physician or pharmacist before taking Vargatef if:

- You suffer or have suffered in the past from liver problems, bleeding problems, particularly recent bleeding in the lungs.
- You have or ever had problems with your kidneys or if an increased amount of protein has been detected in your urine.
- You take anticoagulant medicines (such as warfarin, phenprocoumon, heparin or acetylsalicylic acid) to prevent blood clotting. Treatment with Vargatef may lead to a higher risk of bleeding.

- 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 physician will decide when to resume your treatment with this medicine.
- You have cancer that has spread to the brain.
- You have high blood pressure.
- 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 physician may carry out some blood tests, for example to check your liver function and to determine determine how fast your blood can clot. Your physician will discuss the results of these tests with you and decide whether you can be given Vargatef.

Inform your physician immediately while taking this medicine if:
- You develop diarrhoea. Treatment of diarrhoea immediately at the first signs is important (see section 4 – 'Side effects').
- You vomit or feel sick (nausea).
- 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. These could be symptoms of serious liver problems.
- You develop fever, chills, rapid breathing, or rapid heart rate. These may be signs of infection or blood infection (sepsis) (see section 4 – 'Side effects').
- You experience severe pain in your stomach area, fever, chills, nausea, vomiting, or abdominal rigidity or bloating. These might be symptoms of a hole in the wall of your gut (bowel perforation).
- You experience pain, swelling, reddening or warmth of a limb, or you have chest pain and have difficulty breathing. These might be symptoms of a blood clot in one of your veins.
- You have any acute bleeding.
- You experience chest pressure or pain, especially on the left side of the body, pain in the neck, jaw, shoulder or arm, a fast heartbeat, shortness of breath, nausea or vomiting. These could be symptoms of a heart attack.
- Any side effect you experience gets worse (see section 4 – 'Side effects').

Children and adolescents
Vargatef has not been studied in patients under 18 years old and is therefore not intended for children and adolescents under 18 years old.

Tests and follow-up
Your physician may carry out some blood tests before you start treatment with Vargatef.
Blood counts should be monitored during the treatment, especially when administered in combination with docetaxel. Sometimes blood counts will be monitored at the beginning of each treatment.
Liver function should be monitored during the treatment, at the beginning of each docetaxel treatment cycle, and every month if continuing treatment with Vargatef only. Coagulation function should be monitored during the treatment.

Other medicines and Vargatef:
If you are taking or have recently taken other medicines, including nonprescription medications and nutritional supplements, inform your physician or pharmacist. Particularly if you are taking:

Vargatef 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 – 'Side effects'):
- ketoconazole (used to treat fungal infections)
- erythromycin (an antibiotic used to treat bacterial infections)

Taking 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 epilepsy)
- St. John's Wort (a herbal medicine to treat depression)

Using the medicine and food
Take Vargatef capsules with food (see section 3 – 'How should you use the medicine').

Pregnancy, breastfeeding, and fertility
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, you should consult a physician or pharmacist before starting to take this medicine.
Do not use Vargatef 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 to prevent pregnancy when they start taking Vargatef, while they are taking Vargatef and for at least 3 months after stopping treatment. It is important to discuss the most appropriate method of contraception for you with your physician. Vomiting and/or diarrhoea or other gastrointestinal problems may affect the absorption of hormonal contraceptives, such as birth control pills and reduce their effectiveness. If you experience any of these, contact your physician to discuss a more appropriate method of contraception.
Tell your physician or pharmacist immediately if you become pregnant or think you may be pregnant during treatment with Vargatef.

Breastfeeding
It is not known if the medicine passes into breast milk and could cause harm to a breastfed baby. Therefore, do not breastfeed during the treatment with Vargatef.

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

Driving and using machines
Vargatef may have a minor influence on your ability to drive and use machines. Do not drive or use machines if you suffer from nausea.

Important information about some of the medicine's ingredients
The capsules contain soya lecithin. If you are allergic to peanuts or soy, do not use this medicine.

3. How should you use the medicine?

Always use according to the physician's instructions. You should check with the physician or the pharmacist if you are not sure about your dose or about how to take this medicine.

Do not take Vargatef on the same day as your chemotherapy treatment with docetaxel.
Swallow the capsule whole with water. Do not chew the capsule, because the liquid tastes bitter.
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 dosage and treatment will be determined only by your physician. The recommended dose is four capsules of Vargatef 100 mg per day (total of 400 mg nintedanib per day).

Split your daily dose into two capsules every 12 hours, for example 2 capsules in the morning and 2 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.

Do not exceed the recommended dose.

Dose reduction
If you develop intolerance due to side effects (see section 4 – 'Side effects') your physician may reduce your daily dose of Vargatef.
Do not reduce the dose or stop the treatment yourself without consulting your physician first.

If your physician has stopped your chemotherapy with docetaxel, depending on your clinical condition, your physician may decide to continue your Vargatef treatment.

In all cases, you should take Vargatef at the appropriate dose twice daily with an interval of about 12 hours between the doses with food (for example in the morning and in the evening) at about the same time of the day. Taking the medicine this way ensures that a steady level of Vargatef is maintained in the body throughout the day.

If you have taken an overdose, contact the physician immediately.
If you have taken an overdose, or if a child has accidentally swallowed the medicine, go immediately to a hospital emergency room and bring the medicine package with you.

If you forget to take the medicine
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 physician or pharmacist.
Even if there is an improvement in your health, do not stop treatment with this medicine without consulting the physician.

If you stop taking the medicine
Do not stop taking Vargatef without consulting your physician first. It is important to persist with daily treatment as recommended by the physician. If you do not take this medicine as prescribed by your physician, this cancer treatment may not work properly.

Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take the medicine. Wear glasses if you need them.
If you have any further questions regarding the use of this medicine, consult the physician or the pharmacist.

4. <u>Side effects</u>

As with any medicine, Vargatef may cause side effects in some users. Do not be alarmed by reading the list of side effects. You may not experience any of them.

Pay special attention if you experience any of the following side effects during treatment with Vargatef:
Very common side effects - effects that occur in more than 1 in10 users:

- **Diarrhoea**
  Diarrhoea may lead to a loss of fluids 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 physician immediately. Start appropriate anti-diarrhoeal treatment, e.g. with loperamide, as soon as possible after having contacted your physician.

Common side effects (effects that occur in 1-10 in 100 users):

- **Febrile neutropenia and sepsis**

Treatment with Vargatef may lead to a reduced number of 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 physician immediately if you develop fever, chills, rapid breathing, or rapid heart rate.
During treatment with Vargatef, your physician will regularly monitor your blood counts and examine you for signs of infection, such as inflammation, fever or tiredness.

The following additional side effects have been classified according to their incidence:
Very common side effects – effects that occur in more than 1 in 10 users:

- Diarrhoea – see details above
- Painful, numbness and/or tingling feeling in fingers and toes (peripheral neuropathy)
- Nausea
- 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
- Imbalance of salts in the body
- Increased liver enzyme values (alanine aminotransferase, aspartate aminotransferase, blood alkaline phosphatase) in blood tests
- Hair loss (alopecia)

Common side effects - effects that occur in 1-10 in 100 users:

- Blood poisoning (sepsis) - see details 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 the 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 blood tests
- Weight loss
- Itching
- Headache
- Increased amount of protein in your urine (proteinuria)

Uncommon side effects - effects that occur in 1-10 in 1,000 usesr:

- Occurrence of holes in the wall of your gut (bowel perforation)
- Serious liver problems
- Inflammation of the pancreas (pancreatitis)
- Myocardial infarction
- Renal failure

Side effect whose frequency is not known (their frequency has not been established yet):

- 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)

If you experience any side effect, if any side effect gets worse, or if you suffer from a side effect not mentioned in the leaflet, you should consult the physician.

Reporting side effects
You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link:
https://sideeffects.health.gov.il

5. How to store the medicine?

- Prevent poisoning! This medicine and any other medicine should be kept in a close place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting without an explicit instruction from the physician.
- Do not use the medicine after the expiry date (exp. date) appearing on the carton and blister. The expiry date refers to the last day of that month. If you are in contact with the content of the capsule, wash off your hands immediately with plenty of water (see section 3).

Storage conditions
- Store below 25˚C. Store in the original package in order to protect from moisture.
- Do not use this medicine if the package is damaged or a capsule is broken.
- Do not discard medicines via the household waste or wastewater. Consult the pharmacist about how to dispose of medicines you no longer use. These measures will help protect the environment.

6. Additional information

- In addition to the active ingredient the medicine also contains:
  Capsule fill: Triglycerides, hard fat, lecithin (E322)
  Capsule coating: Gelatin, glycerol, titanium dioxide, iron oxide red, iron oxide yellow, black ink (Opacode®).

- What does the medicine look like and what are the contents of the package:

  Vargatef 100 mg: peach, soft, opaque, oblong capsules imprinted in black on one side with the Boehringer Ingelheim company symbol and the number "100".

  Vargatef 150 mg: brown, soft, opaque, oblong capsules imprinted in black on one side with the Boehringer Ingelheim company symbol and the number "150".

  The capsules are packed in blisters. 10 capsules per blister.
  Package of Vargatef 100 mg contains 60 or 120 capsules per box.
  Package of Vargatef 150 mg contains 60 capsules per box.
  Not all pack sizes may be marketed.

- Manufacturer's name and address: Boehringer Ingelheim Pharma, Ingelheim am Rhein, Germany
- Registration holder and importer: Boehringer Ingelheim Israel Ltd., 89 Medinat Ha-Yehudim, P.O.B. 4124, Hertzliya-Pituach 4676672
- This leaflet was revised in April 2021 according to MOH guidelines.
- Registration number of the medicine in the National Drug Registry of the Ministry of Health:
  Vargatef 100 mg: 154-76-34336-00
  Vargatef 150 mg: 154-77-34338-00