PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

The medicine is dispensed with a doctor's prescription only

Nexavar®
Film-coated Tablets

Each tablet contains:
sorafenib (as tosylate) 200 mg
Inactive and allergenic ingredients: see section 6 "Further Information".

Read the leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed to treat your ailment. 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 THE MEDICINE INTENDED FOR?

Nexavar is intended to treat:
- Patients with advanced renal cell carcinoma
- Patients with hepatocellular carcinoma
- Patients with differentiated thyroid carcinoma

Therapeutic group: Nexavar belongs to a group of medicines called multikinase inhibitors and works by slowing the growth rate of cancerous cells and stopping the blood supply that enables cancerous cells to grow.

2) BEFORE USING THE MEDICINE

Do not use the medicine if:

- You are sensitive (allergic) to sorafenib or to any of the additional ingredients contained in the medicine. For the list of inactive ingredients, see section 6 "Further Information".
- You are breastfeeding.

Special warnings regarding use of the medicine

Talk to your doctor or pharmacist before taking Nexavar.

Before treatment with Nexavar, tell your doctor if:
- **You experience skin problems.** Nexavar may cause rashes and skin reactions, especially on the hands and feet. These can usually be treated by your doctor. If not, your doctor may interrupt treatment or stop it altogether.
- **You have high blood pressure.** Nexavar may increase blood pressure and your doctor will usually monitor your blood pressure and may prescribe you a medicine to treat your 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**.
- **You have diabetes.** Blood sugar levels in diabetic patients should be checked regularly in order to assess if the dosage of anti-diabetes medicines needs to be adjusted to minimize the risk of low blood sugar.
- **You experience any bleeding problems or are taking warfarin or phenprocoumon.** Treatment with Nexavar may lead to increased risk of bleeding. If you are taking warfarin or phenprocoumon, blood thinners to prevent blood clots, there may be a greater risk of bleeding.
- **You have chest pain or heart problems.** Your doctor may decide to interrupt treatment or stop it altogether.
- **You have a heart disturbance,** such as an abnormal electrical signal called "prolongation of the QT interval".
- **You are due to undergo surgery or if you have recently undergone surgery.** Nexavar may affect the way your wounds heal. Usually, treatment with Nexavar will be discontinued if you are undergoing surgery. Your doctor will decide when to resume treatment with Nexavar.
- **You are taking irinotecan or are being given docetaxel,** which are also medicines for cancer. Nexavar may increase the effects, and especially the side effects, of these medicines.
- **You are taking neomycin or other antibiotics.** The effect of Nexavar may decrease.
- **You have a severe liver impairment.** You may experience more severe side effects when taking this medicine.
- **You have impaired kidney function.** Your doctor will monitor your fluid and electrolyte balance.
- **Fertility.** Nexavar may decrease fertility in men and in women alike. If you are concerned, talk to a doctor.
- **Holes in the gut wall** *(gastrointestinal perforation)* may occur during the course of treatment (see section 4 "Side Effects"). In this case, your doctor will interrupt the treatment.
- **You have thyroid cancer.** Your doctor will monitor the levels of calcium and thyroid hormones in your blood.
- **If you experience the following symptoms, contact your doctor right away since it may be a life-threatening condition:** nausea, shortness of breath, irregular pulse, muscle cramps, seizure, cloudy urine and tiredness. These symptoms may be caused by a group of metabolic complications that may occur during the treatment of cancer, caused by the breakdown products of dying cancer cells (*Tumour lysis syndrome (TLS)*) and that may lead to changes in kidney function and acute kidney failure (see also section 4: "Side Effects").

Tell your doctor if any of the above mentioned conditions affect you. You may need to have them treated or your doctor may decide to change the dosage of Nexavar, or stop treatment altogether (also see section 4 "Side Effects").

Children and adolescents

Nexavar has not yet been tested in children and adolescents.

Drug interactions

Some medicines may affect Nexavar, or Nexavar may affect other medicines.
If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. Especially if you are taking:
- Rifampicin, neomycin or other medicines used to treat infections **(antibiotics)**
- St. John's wort, a herbal preparation for treatment of **depression**
- Phenytoin, carbamazepine or phenobarbital, treatments for **epilepsy** and other conditions
- Dexamethasone, a **corticosteroid** used for the treatment of various conditions
- Warfarin or phenprocoumon, anticoagulants used to **prevent blood clots**
- Doxorubicin, capecitabine, docetaxel, paclitaxel and irinotecan, which are **cancer treatments**
- Digoxin, a treatment for mild to moderate **heart failure**

Use of the medicine and food

Swallow Nexavar with a glass of water, without food or with a low-fat or a moderate-fat meal. Do not take this medicine with high-fat meals, as the efficacy of the medicine may be reduced.

If you plan to eat a high-fat meal, take the tablet at least one hour before or two hours after the meal. See section 3 "How should you use the medicine?".

Pregnancy and breastfeeding

Avoid becoming pregnant while you are being treated with Nexavar.

If you may become pregnant, use appropriate contraception during the course of treatment. If you become pregnant during the course of treatment with Nexavar, tell your doctor immediately and he will decide if treatment should be continued.

Do not breastfeed your baby during the course of treatment with Nexavar, since this medicine may interfere with the growth and development of your baby.

Driving and using machines

There is no evidence that Nexavar will affect the ability to drive or operate machines.

Important information about some of the ingredients of the medicine

This medicine contains less than 1 mmol sodium (23 mg) per dose; i.e., it is essentially considered "sodium-free".

3) HOW SHOULD YOU USE THE MEDICINE?

Always use according to your doctor's instructions. Check with your doctor or pharmacist if you are uncertain about your dosage or about how to take this medicine.
- The dosage and treatment regimen will be determined by the doctor only.
- **The usual dosage for adults is generally two 200 mg tablets, twice a day**. This is equivalent to a daily dosage of 800 mg or 4 tablets per day.
- **Mode of administration: Swallow Nexavar tablets with a glass of water,** without food or with a low-fat or a moderate-fat meal. Do not take this medicine with high-fat meals, as the efficacy of the medicine may be reduced. If you plan to eat a high-fat meal, take the tablet at least one hour before or two hours after the meal. Always take this medicine according to the doctor's instructions. Check with your doctor or pharmacist if you are uncertain.
- It is important to take this medicine at about the same times each day, in order to maintain a steady level in the blood.
- Do not crush, split, or chew the tablet because this may affect the medicine's efficacy or safety.
- **Treatment duration:** You will usually continue taking this medicine as long as you are getting clinical benefits from the treatment, and are not suffering from unacceptable side effects.

Do not exceed the recommended dose.

If you accidentally take a higher dosage, inform your doctor immediately.
Tell your doctor immediately if you (or someone else) have taken more than your prescribed dose.

Taking too much Nexavar increases the probability of side effects or their degree of severity, especially diarrhea and skin reactions. Your doctor may instruct you to stop taking the medicine.

If you took an overdose or if a child has accidentally swallowed some medicine, refer immediately to a doctor or proceed to a hospital emergency room, and bring the package of the medicine with you.

If you forget to take the medicine at the specified time, take a dose as soon as you remember. If it is nearly time for the next dose, skip the forgotten dose and continue taking the medicine at the usual time. Do not take a double dose to compensate for a forgotten dose!

Adhere to the treatment regimen as recommended by your doctor.

Even if there is an improvement in your health, do not stop treatment with the medicine without consulting your doctor.

Do not take medicines in the dark! Check the label and the dose each time you take medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4) SIDE EFFECTS

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

Nexavar may also affect the results of some blood tests.

Very common side effects (may affect more than 1 in 10 people):
- Diarrhea
- Nausea
- Feeling weak or tired *(fatigue)*
- Pain (including mouth pain, abdominal pain, headaches, bone pain, pain in the tumor itself)
- Hair loss *(alopecia)*
- Flushed or painful palms of the hands or soles of the feet *(hand-foot skin reaction)*
- Itching or rash
- Vomiting
- Bleeding (including bleeding in the brain, gut wall and respiratory tract)
- High blood pressure or increase in blood pressure *(hypertension)*
- Infections
- Loss of appetite *(anorexia)*
- Constipation
- Joint pain *(arthralgia)*
- Fever
- Weight loss
- Dry skin

Common side effects (may affect up to 1 in 10 people):
- Flu-like illness
- Indigestion *(dyspepsia)*
- Difficulty swallowing *(dysphagia)*
- Inflamed or dry mouth, tongue pain *(stomatitis and mucosal inflammation)*
- Low calcium levels in the blood *(hypocalcemia)*
- Low potassium levels in the blood *(hypokalemia)*
- Low blood sugar level *(hypoglycemia)*
- Muscle pain *(myalgia)*
- Sensation disturbances in the fingers and toes, including tingling or numbness *(peripheral sensory neuropathy)*
- Depression
- Erection problems *(impotence)*
- Voice changes *(dysphonia)*
- Acne
- Inflamed, dry or scaly skin that sheds *(dermatitis, peeling skin)*
- Heart failure
- Heart attack *(myocardial infarction)* or chest pain
- Ringing in the ears *(tinnitus)*
- Kidney failure
- Unusually high protein levels in the urine *(proteinuria)*
- General weakness or loss of strength *(asthenia)*
- Decrease in the number of white blood cells *(leucopenia and neutropenia)*
- Decrease in the number of red blood cells *(anemia)*
- Low number of platelets in the blood *(thrombocytopenia)*
- Inflammation of hair follicles *(folliculitis)*
- Underactive thyroid gland *(hypothyroidism)*
- Low blood sodium levels *(hyponatremia)*
- Disturbance in sense of taste *(dysgeusia)*
- Redness in the face and often in other areas of the skin as well *(flushing)*
- Runny nose *(rhinorrhea)*
- Heartburn *(gastroesophageal reflux)*
- Skin cancer *(keratoacanthoma/squamous cell cancer of the skin)*
- Thickening of the outer layer of the skin *(hyperkeratosis)*
- A sudden, involuntary contraction of a muscle *(a muscle spasm)*

Uncommon side effects (effects that may affect up to 1 in 100 people):
- Inflammation in the lining of the stomach *(gastritis)*
- Abdominal pain caused by pancreatitis, inflammation of the gallbladder and/or bile ducts
- Yellow skin or yellow eyes *(jaundice)* caused by high levels of gallbladder pigment *(hyperbilirubinemia)*
- Allergy-like reactions (including skin reactions and hives)
- Dehydration
- Enlarged breasts *(gynecomastia)*
- Breathing difficulties *(pulmonary disease)*
- Eczema
- Overactive thyroid gland *(hyperthyroidism)*
- Multiple skin rashes *(erythema multiforme)*
- Unusually high blood pressure
- Holes in the gut wall *(gastrointestinal perforation)*
- Reversible swelling in the posterior part of the brain that can be associated with headaches, changes in state of consciousness, convulsions, and vision-related symptoms including loss of vision *(reversible posterior leukoencephalopathy)*
- A sudden, severe allergic reaction *(anaphylactic reaction)*

Rare side effects (effects that may affect up to 1 in 1,000 people):
- Allergic reaction with swelling of the skin (e.g., face, tongue), which may cause breathing or swallowing difficulties *(angioedema)*
- Abnormal heart rhythm *(QT interval prolongation)*
- Liver inflammation, which may cause nausea, vomiting, abdominal pain and jaundice *(drug-induced hepatitis)*
- Sunburn-like rash which may appear on skin previously exposed to radiation and can be severe *(radiation recall dermatitis)*
- Serious reactions of the skin and/or mucous membranes, which may include painful blisters and fever, including extensive detachment of the skin *(Stevens-Johnson syndrome and toxic epidermal necrolysis)*
- Abnormal muscle breakdown manifested by muscle pain and may lead to kidney problems *(rhabdomyolysis)*
- Kidney damage which causes them to leak large amounts of protein *(nephrotic syndrome)*
- Inflammation of the blood vessels in the skin which may cause a rash *(leukocytoclastic vasculitis)*

Side effects of unknown frequency (frequency cannot be estimated from the available data):
- Impaired brain function that can be associated with, for example, drowsiness, behavioral changes, or confusion *(encephalopathy)*
- Enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall *(aneurysm and artery dissections)*
- Nausea, shortness of breath, irregular pulse, muscle cramps, seizure, cloudy urine and tiredness (*Tumour lysis syndrome (TLS)*), see section 2

If a side effect occurs, if one of the side effects worsens, or if you suffer from a side effect not mentioned in the leaflet, consult with the doctor.

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il

5) HOW SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine and any other medicine should be kept in a safe place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.
- Do not store at a temperature that exceeds 25°C.
- Do not dispose of medicines in the wastewater or a household waste bin. Ask the pharmacist how to dispose of medicines that are no longer in use. These measures will help protect the environment.

6) FURTHER INFORMATION

- In addition to the active ingredient, the medicine also contains:
  Tablet core: Croscarmellose sodium, cellulose microcrystalline, hypromellose 5 cP, magnesium stearate, sodium laurilsulfate.
  Tablet coating: Hypromellose 15 cP, macrogol 3350, titanium dioxide (E171), ferric oxide red (E172).
- What the medicine looks like and the contents of the package:
  Nexavar film-coated tablets are red and round with the Bayer cross on one side and "200" on the other side.
  They are provided in a package which indicates the days of the month and contains 112 tablets: four transparent trays that contain 28 tablets each.
- **Registration holder's name and address:** Bayer Israel Ltd., 36 Hacharash St., Hod Hasharon 4527702.
- **Manufacturer's name and address:** Bayer AG, Leverkusen, Germany or Bayer HealthCare Manufacturing S.r.l., Milan, Italy.
- This leaflet was revised in May 2022 according to MOH guidelines.
- Registration number of the medicine in the National Drug Registry of the Ministry of Health: 138 01 31543 00/01