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

The medicine is dispensed with a doctor's prescription only

Stivarga®
Film-coated Tablets

Each tablet contains:
Regorafenib 40 mg

Inactive ingredients and allergens in the preparation: see section 6 "Further Information" and also see section 2 "Important information regarding some of the ingredients of the medicine".

Read this 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 for the treatment of your ailment. Do not pass it on to others. It may harm them even if it seems to you that their ailment is similar.

1) WHAT IS THE MEDICINE INTENDED FOR?

Stivarga contains the active ingredient regorafenib and is intended for the treatment of cancer. The medicine acts by slowing the growth and spread of cancer cells and cutting off the blood supply that allows cancer cells to continue growing.
Stivarga is intended for treatment of the following conditions:

- colon or rectal cancer that has spread to other parts of the body in patients who have been treated in the past with fluoropyrimidine-, oxaliplatin- and irinotecan- based chemotherapy, who have been treated in the past with an anti-VEGF therapy and, in the case of KRAS-wild-type, have been treated in the past with an anti-EGFR therapy.

- gastrointestinal stromal tumor (GIST), which is a certain type of cancer of the stomach and bowel that is not amenable to surgery or has spread to other parts of the body, in patients who have been treated in the past with other anti-cancer medicines (imatinib and sunitinib).

- liver cancer (hepatocellular carcinoma - HCC) in patients who have been treated in the past with another anti-cancer medicine (sorafenib).

Therapeutic group: Stivarga belongs to the group of anti-cancer medicines called protein kinase inhibitors. Protein kinase is a group of enzymes responsible for cellular processes. Stivarga is used to treat cancer by slowing the growth and spread of cancer cells and by cutting off the blood supply that allows cancer cells to grow.

2) BEFORE USING THE MEDICINE

Do not use the preparation if:

you are sensitive (allergic) to the active ingredient regorafenib or to any of the other ingredients contained in the medicine. For the list of inactive ingredients, see section 6 "Further Information".

Special warnings regarding use of the medicine
Before treatment with Stivarga, tell the doctor if:

- **you suffer from liver problems,** including Gilbert's syndrome, with signs of yellowish discoloration of the skin and the whites of the eyes, dark urine, confusion and/or disorientation. Treatment with Stivarga may lead to a higher risk of liver problems. Prior to and during treatment with Stivarga, the doctor will have blood tests performed to monitor your liver function. If your liver function is severely impaired, you must not be treated with Stivarga, as there are no data on treatment with Stivarga in such a situation.
- **you suffer from an infection** accompanied by signs such as high fever, severe cough with or without increased secretion of mucus, severe sore throat, shortness of breath, pain/burning sensation when

urinating, unusual vaginal discharge or irritation, redness, swelling and/or pain in any part of the body. The doctor may temporarily stop your Stivarga treatment.

- **you had or have bleeding problems** and if you are taking warfarin, phenprocoumon or another blood-thinning medicine to prevent the formation of blood clots. Treatment with Stivarga may lead to a higher risk of bleeding. Prior to treatment with Stivarga, the doctor may decide to have blood tests performed. Stivarga may cause severe bleeding in the digestive system such as in the stomach, throat, rectum or intestine, or in the lungs, kidneys, mouth, vagina and/or brain. Get medical help immediately if you experience the following symptoms: passing blood in the stools or black stools, passing blood in the urine, stomach pains, coughing/vomiting up blood.
- **severe stomach and bowel problems occur** (gastrointestinal perforation or fistula), the doctor may decide to discontinue treatment with Stivarga. Get medical treatment immediately if you experience the following symptoms: severe stomach pain or stomach pain that does not go away, vomiting blood, red or black stools.
- **you experience chest pain or have any heart problems.** Prior to and during treatment with Stivarga, the doctor will check your heart function. Get medical help immediately if you experience the following symptoms, as they may be a sign of a heart attack or decreased blood flow to the heart: chest discomfort or pain which may spread beyond the chest toward the shoulders, arms, back, neck, teeth, jaw or stomach - the pain may alternately come and go, shortness of breath, sudden outbreak into a cold sweat, cold and clammy skin, feeling dizzy or passing out.
- **you develop a severe and persistent headache, visual disturbances, seizures, lack of energy, sleepiness, impaired consciousness, or altered mental state** (such as confusion, memory loss or disorientation), refer to the doctor immediately.
- **you have high blood pressure.** Treatment with Stivarga may raise your blood pressure. The doctor will monitor your blood pressure prior to and during treatment. The doctor may give you a medicine to treat 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 or have had damage to the smallest blood vessels (thrombotic microangiopathy [TMA]).** Tell your doctor if you develop fever, fatigue, tiredness, bruising, bleeding, swelling, confusion, vision loss, and seizures.
- **you recently had, or are going to have, a surgical procedure.** Treatment with Stivarga might affect the way wounds heal. There may be a need to stop the treatment two weeks before a planned surgery, until the wounds have healed.
- **you experience skin problems.** Treatment with Stivarga may cause redness, pain, swelling, or blisters on the palms of the hands or soles of the feet. If you notice any change, refer to the doctor. To treat these symptoms, the doctor may recommend using creams and/or using shoe cushions and gloves. If you experience these side effects, the doctor may change the dosage or stop the treatment until your condition improves.

Before taking Stivarga, tell the doctor if the described effects apply to you. You may need treatment or additional tests. See section 4 “Side Effects”.

Children and adolescents
The medicine is not intended to treat children and adolescents under the age of 18 years.

There is no relevant use of Stivarga in children and adolescents in the indication of colon or rectal cancer that has spread to other parts of the body.
In the absence of available data, the safety and efficacy of Stivarga in children and adolescents in the indication of gastrointestinal stromal tumors (GIST) have not been established.
There is no relevant use of Stivarga in children and adolescents in the indication of liver cancer.

Drug interactions
If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. Some medicines may affect the efficacy of Stivarga or Stivarga may affect the efficacy of other medicines and cause serious side effects. Especially, inform the doctor or pharmacist if you are taking:

- Medicines to treat fungal infections (such as ketoconazole, itraconazole, posaconazole, voriconazole).

- Medicines to treat pain (such as mefenamic acid, diflunisal and niflumic acid).
- Medicines to treat bacterial infections (such as rifampicin, clarithromycin, telithromycin).
- Medicines to treat epilepsy (such as phenytoin, carbamazepine or phenobarbital).
- Methotrexate - usually used to treat cancer.
- Rosuvastatin, fluvastatin or atorvastatin - generally used to treat high levels of cholesterol.
- Warfarin or phenprocoumon to thin the blood.
- St. John's wort (*Hypericum*) - a herbal medicine used to treat depression.

Consult the doctor or pharmacist before taking any medicine.

Use of the medicine and food
Avoid drinking grapefruit juice during the course of treatment with Stivarga, as drinking it may affect how the medicine works. Swallow the medicine whole, with water, after a light (low-fat) meal that contains less than 30% fat.
See section 3 "How Should You Use the Medicine?".

Pregnancy, breastfeeding and fertility
Pregnancy:
Inform the doctor if you think you are pregnant, may be pregnant or plan on becoming pregnant.
Do not use Stivarga during pregnancy unless the medicine is clearly necessary. The doctor will explain to you the potential risks of taking Stivarga during pregnancy.
Avoid becoming pregnant during the course of treatment with Stivarga, as the medicine may harm the unborn baby.

Women of childbearing age and men must use effective contraception during the course of treatment and for at least 8 weeks after completion of treatment.

Breastfeeding:
Do not breastfeed during treatment with Stivarga, as the medicine may interfere with the growth and development of your baby.
Tell the doctor if you are breastfeeding or are planning to breastfeed.

Fertility:
Stivarga may reduce fertility in both men and women. Consult with the doctor before commencing treatment.

Driving and operating machinery
It is not known whether treatment with Stivarga alters the ability to drive and operate machines.
Do not drive or use any tools or machines if you experience treatment-related symptoms that affect your ability to concentrate and react until these symptoms have passed.

Important information regarding some of the ingredients of the medicine
Stivarga contains 56.06 mg sodium (main ingredient in table/cooking salt) per daily dose (4 tablets). This amount is equivalent to 3% of the recommended daily intake of sodium in an adult diet.
Stivarga contains 1.68 mg **lecithin** (derived from soya) per daily dose (4 tablets).
See section 6 "Further Information".

3) HOW SHOULD YOU USE THE MEDICINE?

Always use the preparation according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the preparation dosage and treatment regimen.

- The dosage and treatment regimen will be determined by the doctor only. **The usual dosage is generally** 4 Stivarga 40 mg tablets, once a day (160 mg regorafenib). The doctor may change your dosage.
  The doctor will usually instruct you to take Stivarga for 3 weeks, after which there will be a one-week break. This is 1 cycle of treatment.
- Take Stivarga at the same time each day after a light (low-fat) meal containing less than 30% fat. Swallow the tablet whole with water. An example of a light (low-fat) meal: one portion of cereals (approximately 30 g), one cup of skimmed milk, one slice of toast with jam, one glass of apple juice, and one cup of coffee or

tea (520 calories, 2 g fat). Avoid drinking grapefruit juice during the course of treatment with Stivarga; see "Use of the medicine and food" in section 2.

- In case of vomiting after taking Stivarga, do not take another dose. Refer to the doctor.
- If necessary, the doctor may decide to reduce the dosage or temporarily or permanently interrupt the treatment. Stivarga is usually taken as long as there is benefit from the treatment and no unbearable side effects are experienced.
- No dosage adjustment is necessary if you have mildly impaired liver function. If you have mildly or moderately impaired liver function while being treated with Stivarga, the doctor must closely monitor liver function. If your liver function is severely impaired, you must not be treated with Stivarga, as there are no data regarding treatment with Stivarga in this situation.
- No dosage adjustment is necessary if you have mildly, moderately or severely impaired kidney function.

Do not exceed the recommended dose.

Method of administration:
There is no information regarding crushing/halving/chewing.

If you have accidentally taken a dosage higher than what has been prescribed for you, inform your doctor immediately. You may need medical attention and your doctor will tell you to stop treatment with Stivarga.
Taking too high a dosage of Stivarga may cause certain side effects to be more likely to occur or to be more severe, especially:

- skin reactions (rash, blisters, redness, pain, swelling, itching or peeling of the skin)
- dysphonia (voice changes, hoarseness)
- diarrhea
- mouth sores (mucosal inflammation)
- dry mouth
- decreased appetite
- hypertension
- excessive tiredness

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

If you forget to take this medicine at the required time, take a dose as soon as you remember on the same day. Do not take a double dose of Stivarga on the same day to compensate for a dose forgotten on the previous day. Tell the doctor about any forgotten dose.
Adhere to the treatment as recommended by the 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 Stivarga may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them. This medicine may also affect the results of certain blood tests.

The most serious side effects, for which a fatal outcome has been observed, are: severe liver problems (including liver failure), bleeding, gastrointestinal perforation and infection.

Refer to the doctor immediately if you experience any of the following effects:

- **Liver problems:** Treatment with Stivarga may lead to an increased risk of severe liver problems. Get medical treatment immediately if you experience the following symptoms:
  - yellowish discoloration of the skin and the whites of the eyes
  - dark urine
  - confusion and/or disorientation

These may be signs of severe liver injury.

- **Bleeding:** Stivarga may cause severe bleeding in the digestive system, such as: in the stomach, throat, rectum or intestine, or in the lungs, kidneys, mouth, vagina and/or brain. Get medical treatment immediately if you experience the following symptoms:
  - presence of blood in the stools or black stools
  - presence of blood in the urine
  - stomach pain
  - coughing/vomiting up blood

These may be signs of bleeding.

- **Severe stomach and bowel problems (gastrointestinal perforation or fistula):** Get medical treatment immediately if you experience the following symptoms:
  - severe stomach pain or stomach pain that does not go away
  - vomiting blood
  - red or black stools

These may be signs of severe stomach or bowel problems.

- **Infection:** Treatment with Stivarga may lead to increased risk of infections, especially infections of the urinary tract, nose, throat and lungs. Treatment with Stivarga may also lead to increased risk of fungal infections of the mucous membranes, skin or body. Get medical help immediately if you experience the following symptoms:
  - high fever
  - severe cough, with or without increased secretion of mucus
  - severe sore throat
  - shortness of breath
  - pain/burning sensation when urinating
  - unusual vaginal discharge or irritation
  - redness, swelling and/or pain in any part of your body

These may be signs of an infection.

Additional side effects

Very common side effects (may affect more than 1 in 10 users):

- reduction in the number of blood platelets, characterized by occurrence of easy skin bruising or bleeding (thrombocytopenia)
- reduction in the number of red blood cells (anemia)
- decreased appetite and food intake
- hypertension
- voice changes, hoarseness (dysphonia)
- diarrhea
- painful or dry mouth, painful tongue, mouth sores (stomatitis and/or mucosal inflammation)
- nausea
- vomiting
- high blood levels of bilirubin, a substance produced by the liver (hyperbilirubinemia)
- changes in enzymes produced by the liver, which may indicate liver damage (increase in transaminases)
- redness, pain, blisters and swelling of the palms of the hands or soles of the feet (hand-foot skin reaction)
- rash
- weakness, lack of strength or energy, excessive tiredness and unusual sleepiness (fatigue)
- pain (including abdominal pain and back pain)
- constipation
- fever
- weight loss

Common side effects (may affect up to 1 in 10 users):

- reduction in the number of white blood cells (leukopenia)
- decreased activity of the thyroid gland (hypothyroidism)

- low levels of potassium, phosphate, calcium, sodium or magnesium in the blood (hypokalemia, hypophosphatemia, hypocalcemia, hyponatremia and hypomagnesemia)
- high levels of uric acid in the blood (hyperuricemia)
- dehydration (loss of fluids)
- headaches
- tremor
- nerve disorder that may cause a change in sensation, such as numbness, weakness or pain (peripheral neuropathy)
- taste disorders
- dry mouth
- heartburn (gastroesophageal reflux)
- infection or irritation of the stomach and intestines (gastroenteritis)
- hair loss (balding)
- dry skin
- rash with peeling of skin
- sudden, involuntary contraction of a muscle (spasm)
- presence of protein in the urine (proteinuria)
- high levels of certain enzymes involved in digestion (increase in amylase and lipase)
- blood clotting disturbance (abnormal INR - International Normalized Ratio)

Uncommon side effects (may affect up to 1 in 100 users):
- signs/symptoms of a sensitivity reaction (allergy) which may include severe, widespread rash, nausea, fever, breathlessness, jaundice, changes in substances produced by the liver
- heart attack, chest pain (myocardial infarction and ischemia)
- significantly elevated blood pressure causing headache, confusion, blurry vision, nausea, vomiting, epileptic fits (hypertensive crisis)
- inflammation of the pancreas characterized by pain in the stomach area, nausea, vomiting and fever (pancreatitis)
- nail disease (changes to the nail such as: ridges and/or splitting of the nail)
- rash (erythema multiforme)

Rare side effects (may affect up to 1 in 1,000 users):
- blood clots in small blood vessels (*thrombotic microangiopathy*)
- certain types of skin cancer (squamous cell carcinoma/keratoacanthoma)
- headaches, confusion, seizures and visual loss sometimes associated with increased blood pressure (posterior reversible encephalopathy syndrome/PRES)
- 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)

Side effects whose frequency is not known (frequency cannot be estimated from the available data):
- enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections)
- lack of energy, confusion, sleepiness, trembling, impaired consciousness – these symptoms may be signs of brain toxicity caused by high blood levels of ammonia (*hyperammonemic encephalopathy*).

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 must 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.
- Keep the bottle tightly closed after first opening and leave the desiccants in the bottle.
- Dispose of the medicine 7 weeks after first opening the bottle.
- Do not dispose of the medicine in the waste bin or wastewater. Ask the pharmacist how to dispose of medicines you no longer use.
- Do not store at a temperature exceeding 30°C. Keep the medicine in its original package to protect from moisture.

6) FURTHER INFORMATION

- In addition to the active ingredient, the medicine also contains:
  Tablet:
  povidone, croscarmellose sodium, cellulose microcrystalline, magnesium stearate, silica colloidal anhydrous.
  Tablet coating:
  lacquer pink (Opadry II™ 85G35294 pink): polyvinyl alcohol (partially hydrolyzed), talc, titanium dioxide (E171), macrogol/PEG 3350, lecithin (soya), ferric oxide yellow (E172), ferric oxide red (E172).
  Each tablet contains 14 mg sodium.

- What does the medicine look like and what are the contents of the package?
  Stivarga 40 mg tablets are film-coated, light pink, oval, with the word “Bayer” embossed on one side and “40” on the other side. Stivarga tablets are packaged in a white plastic bottle that contains 28 tablets. The package size can include one plastic bottle or a pack of 3 plastic bottles (total of 84 tablets).

- **Registration Holder and Address:** Bayer Israel Ltd., 36 Hacharash St., Hod Hasharon 4527702.

- **Manufacturer and Address:** Bayer AG, Leverkusen, Germany.

- Revised in July 2025.

- Registration number of the medicine in the National Drug Registry of the Ministry of Health:
  150 87 33823 00

STIV CTAB PL SH 220623