Package Leaflet: Information for the user

Stivarga 40 mg film-coated tablets
regorafenib

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 Stivarga is and what it is used for
2. What you need to know before you take Stivarga
3. How to take Stivarga
4. Possible side effects
5. How to store Stivarga
6. Contents of the pack and other information

1. What Stivarga is and what it is used for

Stivarga contains the active substance regorafenib. It is a medicine used to treat cancer by slowing down the growth and spread of cancer cells and cutting off the blood supply that keeps cancer cells growing.

Stivarga is used to treat:
- colon or rectal cancer that has spread to other parts of the body in adult patients who have received other treatments or cannot be treated with other medicines (fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy)
- gastrointestinal stromal tumours (GIST), a type of cancer of the stomach and bowel, that has spread to other parts of the body or is not amenable to surgery, in adult patients who have been previously treated with other anticancer medicines (imatinib and sunitinib)
- liver cancer in adult patients who have been previously treated with another anticancer medicine (sorafenib).

If you have any questions about how Stivarga works or why this medicine has been prescribed for you, please ask your doctor.

2. What you need to know before you take Stivarga

Do not take Stivarga
- if you are allergic to regorafenib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking Stivarga.

Take special care with Stivarga

- **if you have any liver problems** including Gilbert's syndrome with signs such as: yellowish discolouration of the skin and the whites of the eyes, dark urine and confusion and/or disorientation. Treatment with Stivarga may lead to a higher risk of liver problems. Prior to and during treatment with Stivarga, your doctor will do blood tests to monitor your liver function. If your liver function is severely impaired, you should not be treated with Stivarga, as there are no data on the use of Stivarga in patients with a severely impaired liver function.

- **if you get an infection** with signs such as high fever, severe cough with or without an increase in mucus (sputum) production, severe sore throat, shortness of breath, burning/pain when urinating, unusual vaginal discharge or irritation, redness, swelling and/or pain in any part of the body. Your doctor may temporarily stop your treatment.

- **if you had or have any bleeding problems** and if you are taking warfarin, phenprocoumon or another medicine that thins the blood to prevent blood clots. Treatment with Stivarga may lead to a higher risk of bleeding. Before you start taking Stivarga your doctor may decide to do blood tests. Stivarga can cause severe bleeding in the digestive system such as stomach, throat, rectum or intestine, or in the lungs, kidneys, mouth, vagina and/or brain. Get medical help immediately, if you get the following symptoms: passing blood in the stools or passing black stools, passing blood in the urine, stomach pain, coughing/vomiting up blood.

- **if you get severe stomach and bowel problems** (gastrointestinal perforation or fistula), your doctor should decide to discontinue treatment with Stivarga. Get medical help immediately, if you get the following symptoms: severe stomach pain or stomach pain that does not go away, vomiting blood, red or black stools.

- **if you get chest pain or have any heart problems**. Before you start taking Stivarga and during treatment your doctor will check how well your heart is working. Get medical help immediately if you get the following symptoms, as they may be signs of a heart attack or decreased blood flow to the heart: chest discomfort or pain which may spread beyond your chest to your shoulders, arms, back, neck, teeth, jaw or stomach and may come and go; shortness of breath; sudden outbreak into a sweat with cold, clammy skin, feeling dizzy or fainting.

- **if you develop a severe and persistent headache, visual disturbances, seizures, lack of energy, sleepiness, impaired consciousness or altered mental status** (such as confusion, memory loss or loss of orientation) please contact your doctor immediately.

- **if you have high blood pressure** Stivarga can raise your blood pressure. Your doctor will monitor your blood pressure prior to and during treatment and may give you a medicine to treat 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**.

- **if 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.

- **if you recently had, or are going to have, a surgical procedure** Stivarga might affect the way your wounds heal and treatment may need to be stopped until your wound have healed.

- **if you experience skin problems** Stivarga can cause redness, pain, swelling, or blisters on the palms of your hands or soles of your feet. If you notice any changes contact your doctor. To manage your symptoms, your doctor may recommend the use of creams and/or the use of shoe cushions and gloves. If you get this side effect, your doctor may change your dose or stop your treatment until your condition improves.

Before you take Stivarga **tell your doctor if any of these conditions apply to you.** You may need treatment for them and extra tests may be done (see also section 4 'Possible side effects').

Children and adolescents
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.
The safety and efficacy of Stivarga in children and adolescents in the indication of gastrointestinal stromal tumours (GIST) have not been established. No data are available.
There is no relevant use of Stivarga in children and adolescents in the indication of liver cancer.

Other medicines and Stivarga

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription or even over-the-counter medicines, such as vitamins, dietary supplements or herbal medicines. Some medicines may affect the way Stivarga works or Stivarga may affect how other medicines work and cause serious side effects. In particular, tell your doctor if you are taking anything in this list or any other medicines:
- some medicines to treat fungal infections (e.g. ketoconazole, itraconazole, posaconazole and voriconazole)
- some medicines to treat pain (e.g. mefenamic acid, diflunisal, and niflumic acid)
- some medicines to treat bacterial infections (e.g. rifampicin, clarithromycin, telithromycin)
- medicines typically used to treat epilepsy (seizures) (e.g. phenytoin, carbamazepine or phenobarbital)
- methotrexate, a medicine typically used to treat cancer
- rosuvastatin, fluvastatin, atorvastatin, medicines typically used to treat high cholesterol
- warfarin or phenprocoumon, medicines typically used to thin your blood
- St. John's wort (medicine obtained also without a prescription), a herbal treatment for depression.

Ask your doctor or pharmacist for advice before taking any medicine.

Taking Stivarga with food and drink
Avoid drinking grapefruit juice while taking Stivarga. This can affect the way Stivarga works.

Pregnancy, breast-feeding and fertility
Tell your doctor if you think you are pregnant, may be pregnant or plan on becoming pregnant as Stivarga should not be used during pregnancy unless clearly necessary. Your doctor will discuss with you the potential risks of taking Stivarga during pregnancy.

Avoid becoming pregnant while being treated with Stivarga, as this medicine may harm your unborn baby.

Both women of childbearing potential and men should use effective contraception during treatment and for at least eight weeks after completion of treatment.

You must not breast-feed your baby during Stivarga treatment, as this medicine may interfere with the growth and development of your baby. **Tell your doctor if you are breast-feeding or planning to breast-feed.**

Stivarga may reduce fertility in both men and women. Ask your doctor for advice before taking Stivarga.

Driving and using machines
It is not known whether Stivarga alters the ability to drive or use machines. Do not drive or use any tools or machines if you experience treatment-related symptoms that affect your ability to concentrate and react.

Important information about some of the ingredients of Stivarga
This medicine contains 56.06 mg sodium (main component of cooking/table salt) in each daily dose (4 tablets). This is equivalent to 3% of the recommended maximum daily dietary intake of sodium for an adult.

This medicine contains 1.68 mg of **lecithin** (derived from soya) per daily dose (4 tablets).

3. How to take Stivarga

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

The recommended daily dose in adults is 4 tablets of Stivarga 40 mg (160 mg regorafenib). Your doctor may change your dose. Take the dose of Stivarga that your doctor prescribes for you.
Your doctor will usually ask you to take Stivarga for 3 weeks and then to stop for 1 week. This is 1 cycle of treatment.

Take Stivarga at the same time each day after a light (low-fat) meal. Swallow the tablet whole with water after a light meal that contains less than 30% fat. An example of a light (low-fat) meal would include 1 portion of cereal (about 30 g), 1 glass of skimmed milk, 1 slice of toast with jam, 1 glass of apple juice, and 1 cup of coffee or tea (520 calories, 2 g fat). You should not take Stivarga together with grapefruit juice (see also section ‘Taking Stivarga with food and drink’).

In case of vomiting after regorafenib administration, you should not take additional tablets and you should inform your doctor.

Your doctor may need to reduce your dose or may decide to interrupt or discontinue the treatment permanently if necessary. You will usually take Stivarga as long as you are benefiting and not suffering unacceptable side effects.

No dosage adjustment is necessary if you have a mildly impaired liver function. If you have a mildly or moderately impaired liver function while you are being treated with Stivarga, your doctor should monitor you closely. If your liver function is severely impaired, you should not be treated with Stivarga, as there are no data on the use of Stivarga in patients with a severely impaired liver function.

No dosage adjustment is necessary if you have a mildly, moderately or severely impaired kidney function.

If you take more Stivarga than you should
Tell your doctor immediately if you have taken more than your prescribed dose. You may require medical attention and your doctor may tell you to stop taking Stivarga.

Taking too much Stivarga may make some side effects more likely or more severe, especially:
- skin reactions (rash, blisters, redness, pain, swelling, itching or peeling of your skin)
- voice changes or hoarseness (*dysphonia*)
- frequent or loose bowel movements (*diarrhoea*)
- mouth sores (*mucosal inflammation*)
- dry mouth
- decreased appetite
- high blood pressure (*hypertension*)
- excessive tiredness (*fatigue*).

If you forget to take Stivarga
If you miss a dose, take it as soon as you remember on that day. Do not take two doses of Stivarga on the same day to make up for a missed dose from the previous day. Tell your doctor about any missed dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. This medicine may also affect the results of some 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.

Tell your doctor immediately if you have any of the following symptoms:

Liver problems
Treatment with Stivarga may lead to a higher risk of severe liver problems. Get medical help immediately if you get the following symptoms:
- yellowish discolouration 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 can cause severe bleeding in the digestive system such as stomach, throat, rectum or intestine, or in the lungs, kidneys, mouth, vagina and/or brain. Get medical help immediately, if you get the following symptoms:
- passing blood in the stools or passing black stools
- passing 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 help immediately, if you get the following symptoms:
- severe stomach (abdominal) 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 a higher risk of infections, especially of the urinary tract, nose, throat and lung. Treatment with Stivarga may also lead to a higher risk of fungal infections of the mucous membrane, skin or the body. Get medical help immediately if you get the following symptoms:
- high fever
- severe cough with or without an increase in mucus (sputum) production
- severe sore throat
- shortness of breath
- burning/pain when urinating
- unusual vaginal discharge or irritation
- redness, swelling and/or pain in any part of the body.

These may be signs of an infection.
Other side effects with Stivarga listed by frequency:

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

- reduction in the number of blood platelets, characterised by easy bruising or bleeding (*thrombocytopenia*)
- reduction in the number of red blood cells (*anaemia*)
- decreased appetite and food intake
- high blood pressure (*hypertension*)
- voice changes or hoarseness (*dysphonia*)
- frequent or loose bowel movements (*diarrhoea*)
- painful or dry mouth, painful tongue, mouth sores (*stomatitis and/or mucosal inflammation*)
- feeling sick (*nausea*)
- vomiting
- high blood levels of bilirubin, a substance produced by the liver (*hyperbilirubinaemia*)
- changes in enzymes produced by the liver, which may indicate that something is wrong with the liver (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 and energy, excessive tiredness and unusual sleepiness *(asthenia/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 (*leucopenia*)
- decreased activity of the thyroid gland (*hypothyroidism*)
- low levels of potassium, phosphate, calcium, sodium or magnesium in your blood (*hypokalaemia, hypophosphatemia, hypocalcaemia, hyponatraemia and hypomagnesaemia*)
- high level of uric acid in the blood (hyperuricaemia)
- loss of body fluids (*dehydration*)
- headache
- shaking (*tremor*)
- disorder of the nerves which can cause a change in sensation, such as numbness, tingling, weakness or pain (*peripheral neuropathy*)

- taste disorders
- dry mouth
- heartburn (*gastro-oesophageal reflux*)
- infection or irritation of the stomach and intestines (gastroenteritis)
- hair loss (*alopecia*)
- dry skin
- rash with flaking or peeling of skin *(exfoliative rash)*
- a sudden, involuntary contraction of a muscle (*muscle spasms*)
- protein in the urine (*proteinuria)*
- high levels of certain enzymes involved in digestion (*increase in amylase and lipase*)
- abnormal blood clotting condition (*abnormal International Normalized Ratio*).

Uncommon side effects (may affect up to 1 in 100 users)

- signs/symptoms of an allergic reaction which may include widespread severe rash, feeling sick, fever, breathlessness, jaundice, changes in chemicals produced by the liver (*hypersensitivity reaction*)
- heart attack, chest pain (*myocardial infarction and ischaemia*)
- severely elevated blood pressure causing headache, confusion, blurry vision, nausea, vomiting, and fits (*hypertensive crisis*)
- inflammation of the pancreas characterized by pain in the area of the stomach, nausea, vomiting, and fever (pancreatitis)
- nail disorder (changes to the nail such as ridges and/or splitting)
- multiple skin eruptions (*erythema multiforme*).

Rare side effects (may affect up to 1 in 1,000 users)

- blood clots in small blood vessels (thrombotic microangiopathy)
- certain skin cancers (*keratoacanthoma/squamous cell carcinoma of the skin*)
- headache, confusion, seizures and visual loss associated with or without high 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*).

Not known (frequency cannot be estimated from the available data)

- an 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 (*hyperammonaemic encephalopathy)*.

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 the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Stivarga

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 the bottle label after EXP. The expiry date refers to the last day of that month.

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

Keep the bottle tightly closed.

Once the bottle is opened the medicine is to be discarded after 7 weeks.

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 Stivarga contains
- The **active** substance is regorafenib. Each film-coated tablet contains 40 mg regorafenib.
- The **other** ingredients are: cellulose microcrystalline, croscarmellose sodium, magnesium stearate, povidone (K-25) and silica colloidal anhydrous, iron oxide red (E172), iron oxide yellow (E172), lecithin (derived from soya), macrogol 3350, polyvinyl alcohol (partially hydrolysed), talc and titanium dioxide (E171) (see also section 'Important information about some of the ingredients of Stivarga').

What Stivarga looks like and contents of the pack
Stivarga 40 mg tablets are light pink and oval, marked with "BAYER" on one side and "40" on the other side.

Each bottle contains 28 film-coated tablets.

Stivarga 40 mg tablets are available in packs containing one bottle or three bottles.

Not all pack sizes may be marketed.

Keep the desiccant in the bottle. The desiccant is a moisture absorbing material filled in a small container to protect the tablets from moisture.

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