SELECT THE REQUIRED INFORMATION

PROFESSIONAL INFORMATION

PATIENT INFORMATION LEAFLET

Bayer (Pty) Ltd	**Approved date: 01 June 2020**

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S4

STIVARGA® 40 mg FILM-COATED TABLET
Regorafenib
Sugar free

Read all of this leaflet carefully before you start taking STIVARGA.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- STIVARGA has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet

1. **What STIVARGA is 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 patients who have received other treatments or cannot be treated with other medicines (fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if RAS wild type, an anti-EGFR therapy).
- gastrointestinal stromal tumors (GIST), a type of cancer of the stomach and bowel, in patients who have been previously treated with other anticancer medicines (2 tyrosine kinase inhibitors)
- liver cancer in patients who have been previously treated with another anticancer medicine

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 hypersensitive (allergic) to regorafenib or any of the other ingredients of STIVARGA.
- if you are pregnant or planning to become pregnant.
- if you are breastfeeding your baby.
- if you have severe stomach and bowel problems

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 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 the treatment with STIVARGA your doctor will do blood tests to monitor your 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 or a medicine that thins the blood to prevent blood clots. Treatment with STIVARGA may lead to a higher risk of bleeding. Before you start STIVARGA your doctor may decide to do blood tests.
- **If you get severe stomach and bowel problems**, your doctor will discontinue treatment with STIVARGA. Get medical help immediately, if you get the following symptoms: severe stomach or bowel pain or stomach or bowel 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 STIVARGA and during treatment your doctor will check how well your heart is working.
- **If you develop a severe and persistent headache, visual disturbances, seizures or altered mental status** (such as confusion, memory loss or loss of orientation), that may be associated with increased blood pressure, please contact your doctor immediately.
- **If you have high blood pressure.** STIVARGA can raise your blood pressure, and your doctor will monitor your blood pressure prior to and during the treatment and may give you a medicine to treat high blood pressure.
- **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 temporarily stopped before surgery and until your wound has 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 or thickening of the outer layer of your skin. If you notice any changes, be sure to 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 use 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 Possible Side Effects).

Other medicines and STIVARGA

Always tell your healthcare provider if you are taking any other medicine. (This includes all complementary or traditional 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 any of the following medicines:

- ketoconazole, itraconazole, posaconazole, voriconazole - typically used to treat fungal infections
- rifampin, clarithromycin, telithromycin - typically used to treat bacterial infections
- phenytoin, carbamazepine or phenobarbitone - typically used to treat epilepsy (seizures)
- methotrexate - typically used to treat cancer, psoriasis and autoimmune diseases
- rosuvastatin, fluvastatin, atorvastatin - typically used to treat high cholesterol
- warfarin - typically used to thin your blood

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

Pregnancy, breastfeeding, fertility

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other health care provider for advice before taking this medicine.

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.

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

You must not breastfeed your baby during STIVARGA treatment, as it may interfere with the growth and development of your baby. Tell your doctor if you are breastfeeding or planning to breastfeed.

Driving and using machines
STIVARGA may cause tremor and fatigue that may impair your ability to drive or use machines.
It is not always possible to predict to what extent STIVARGA may interfere with your daily activities. Please ensure that you do not engage in the above activities until you are aware of the measure to which STIVARGA affects them.

Important information about some ingredients of STIVARGA
This medicine contains 55.8 mg of sodium (main component of cooking/table salt) per daily dose (4 tablets). To be taken into consideration by patients on a controlled sodium diet.

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

3. HOW TO TAKE STIVARGA:

Do not share medicines prescribed for you with any other person.

Always take STIVARGA exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

The recommended daily dose in adults is 4 x STIVARGA 40 mg tablets (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. Swallow the tablets whole with water after a light (low-fat) meal. You should not take STIVARGA together with grapefruit juice (see also section 'Taking Stivarga with food and drink').

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 benefitting and not suffering unacceptable side effects.

STIVARGA is eliminated mainly by the liver. No dosage adjustment is necessary if you have a mildly or moderately impaired liver function. If you have a mildly or moderately impaired liver function, your doctor should monitor you closely while you are being treated with STIVARGA. 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:

In the event of overdosage, consult your doctor or pharmacist. If neither is available, seek help at the nearest hospital or poison control centre.

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).
- dysphonia (voice changes or hoarseness).
- diarrhoea (frequent or loose bowel movements).
- mucosal inflammation (mouth sores).
- dry mouth.
- decreased appetite.
- hypertension (high blood pressure).
- fatigue (excessive tiredness).

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**

STIVARGA can have side effects.

Not all side effects reported for STIVARGA are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking STIVARGA, please consult your health care provider for advice.

STIVARGA 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 injury, 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 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 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,
- menstrual bleeding that is heavier than normal,
- unusual vaginal bleeding,
- frequent nose bleeds.

These may be signs of bleeding.

Gastrointestinal perforation or fistula (severe stomach and bowel problems)

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 gastrointestinal perforation or fistula (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.

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if notice the following:

Frequent side effects:

pain; hand-foot skin reaction (redness, pain, blisters and swelling of the palms of the hands or soles of the feet, thickening of the outer layer of your skin), asthenia/fatigue (weakness, lack of strength and energy, excessive tiredness and unusual sleepiness); diarrhoea (frequent or loose bowel movements); decreased appetite and food intake; hypertension (high blood pressure); infection; thrombocytopenia (reduction in the number of blood platelets, characterized by easy bruising or bleeding); anaemia (reduction in the number of red blood cells); headache; bleeding; stomatitis and/or mucosal inflammation (painful or dry mouth, painful tongue, mouth sores); nausea (feeling sick); vomiting; hyperbilirubinaemia (high blood levels of bilirubin, a substance produced by the liver, your eyes and skin may turn yellow); rash; pain; fever; weight loss; headache; tremor (shaking); taste disorders; gastroesophageal reflux (heartburn); gastroenteritis (infection or irritation of the stomach and intestines); alopecia (hair loss); dry skin; muscle spasms (a sudden, involuntary contraction of a muscle), exfoliative rash (rash with flaking or peeling if the skin).

Frequent side effects that may show up in your blood or urine tests:

- increase in transaminases (changes in enzymes produced by the liver, which may indicate that something is wrong with the liver),
- leukopenia (reduction in the number of white blood cells),
- hypothyroidism (decreased activity of the thyroid gland),
- hypokalaemia, hypophosphatemia, hypocalcaemia, hyponatremia and hypomagnesaemia (low levels of potassium, phosphate, calcium, sodium or magnesium in your blood),
- hyperuricaemia (high level of uric acid in the blood),
- proteinuria (protein in the urine),
- increase in amylase and lipase (high levels of certain enzymes involved in digestion),
- abnormal International Normalized Ratio (abnormal blood clotting condition).

Less frequent side effects in patients receiving STIVARGA include:

- hypersensitive reaction (allergic reaction),
- myocardial infarction and ischaemia (heart attack, chest pain),
- hypertensive crisis (severely elevated blood pressure causing headache, confusion, blurry vision, nausea, vomiting, and fits),
- gastrointestinal perforation and fistula (severe stomach problems characterised by frequent or loose bowel movements, dehydration, severe pains in your stomach, fever, chills, nausea or vomiting),
- pancreatitis (inflammation of the pancreas characterized by pain in the area of the stomach, nausea, vomiting and fever),
- severe liver injury (signs are yellowish discolouration of the skin and the whites of the eyes, dark urine, excessive tiredness and unusual sleepiness, nausea or vomiting or loss of appetite, confusion and/or disorientation, bruise easily and/or pain on the right side of your stomach),
- nail disorder (changes to the nail such as ridges and/or splitting),
- erythema multiforme (multiple skin eruptions),
- keratoacanthoma / squamous cell carcinoma of the skin (certain skin cancer),
- reversible posterior leukoencephalopathy syndrome / RPLS (signs are severe and persistent headache, visual disturbances, seizures or altered mental status (such as confusion, memory loss or loss of orientation that is often associated with increased blood pressure),

- Stevens-Johnson syndrome and toxic epidermal necrolysis (serious reactions of the skin and/or mucous membranes which may include painful blisters and fever, including extensive detachment of the skin).

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects
If you get side effects, talk to your doctor or pharmacist or nurse. You can also report side effects to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of STIVARGA.

5. How to store STIVARGA

Store all medicines out of reach and sight of children.
Store at or below 30 ˚C.
Store in the original package in order to protect from moisture.

Keep the bottle tightly closed after first opening and keep the desiccant in the bottle.

Once the bottle is opened the medicine has shown to be stable for 7 weeks. Thereafter, the product is to be discarded.

Do not use after the expiry date stated on the bottle.

Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

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:
- Tablet core: cellulose microcrystalline, croscarmellose sodium, magnesium stearate, povidone and silica, colloidal anhydrous
- Film coat: iron oxide red (E 172), iron oxide yellow (E 172), lecithin (derived from soy), macrogol, polyvinyl alcohol (partially hydrolyzed), talc and titanium dioxide (E 171)

Instructions for use / handling
Press down the child resistant cap according to instructions on the cap while turning to the left. The desiccant capsule must not be consumed.

What STIVARGA looks like and contents of the pack
STIVARGA 40 mg film-coated 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 pack containing one bottle or three bottles.
Not all pack sizes may be marketed.

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

Holder of certificate of registration

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