Stivarga® 40 mg film-coated tablets (regorafenib)
Prescribing Information (Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: Each film-coated tablet contains 40 mg regorafenib. **Indication(s):** As monotherapy for the treatment of adult patients with: 1. metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR; 2. unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib; 3. hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. **Posology & method of administration:** Treatment should be prescribed by physicians experienced in the administration of anticancer therapy. ***Adults*:** 160 mg (4 tablets of 40 mg) taken once daily for 3 weeks followed by 1 week off therapy. This 4-week period is considered a treatment cycle. Regorafenib should be taken at the same time each day and should be swallowed whole with water after a light meal that contains less than 30% fat. In case of vomiting after regorafenib administration, the patient should not take additional tablets. Treatment should continue as long as benefit is observed or until unacceptable toxicity occurs. ***Hepatic impairment*:** No dose adjustment is required in patients with mild hepatic impairment. Limited data available in patients with moderate hepatic impairment (Child-Pugh B). Not recommended for use in patients with severe hepatic impairment (Child-Pugh C) as no data available. ***Renal impairment*:** No dose adjustment is required in patients with mild, moderate or severe renal impairment. ***Elderly patients*:** No special considerations are needed. ***Gender*:** No dose adjustment is necessary. ***Ethnicity*:** A higher incidence of hand foot skin reaction (HSFR)/palmar-plantar erythrodysesthesia syndrome has been observed in Asian patients. No dose adjustment is necessary. ***Children & adolescents*:** No data available. **Contra-indications:** Hypersensitivity to regorafenib or any of the excipients. **Warnings & precautions:** Abnormalities of liver function tests have been frequently observed in patients. In clinical trials, a higher incidence of severe liver function test abnormalities and hepatic dysfunction was observed in Asian (in particular Japanese) patients treated with Stivarga as compared with Caucasians. Liver function tests should be performed before initiation of therapy and monitored closely during the first two months of treatment, and periodically thereafter or as indicated. Patients with observed worsening of liver function tests may require dose modifications. See SmPC for further details. Mild, indirect (unconjugated) hyperbilirubinaemia may occur in patients with Gilbert's syndrome. Increased incidence of haemorrhagic events. Increased incidence of infection events. In cases of worsening infection events, interruption of Stivarga treatment should be considered. Blood counts and coagulation parameters should be monitored in patients with conditions predisposing to bleeding, and in those treated with anticoagulants (e.g. warfarin and phenprocoumon) or other concomitant medicinal products that increase the risk of bleeding. Patients with oesophageal varices should be evaluated and treated as per standard of care/guidelines before starting treatment with Stivarga. Gastrointestinal perforation (including fatal outcome) and fistulae have been reported in patients treated with regorafenib: discontinuation of treatment is recommended in patients developing gastrointestinal perforation or fistula. Increased incidence of myocardial ischaemia and infarction: interruption of treatment is recommended in patients developing cardiac ischaemia/infarction. Posterior reversible encephalopathy syndrome (PRES) has been reported in association with regorafenib treatment. Increased incidence of arterial hypertension has been associated with treatment. Blood pressure should be controlled prior to initiation of treatment. Blood pressure should be monitored and hypertension should be treated. In severe or persistent hypertension despite adequate medical management, treatment should be temporarily interrupted and/or the dose reduced at the discretion of the physician. In case of hypertensive crisis, Stivarga should be discontinued. The risk of aneurysm and/or artery dissection should be carefully considered in patients with risk factors such as hypertension or a history of aneurysm before initiating Stivarga. Thrombotic microangiopathy (TMA), including thrombotic thrombocytopaenic purpura (TTP), have been reported: after diagnosis, Stivarga should be discontinued. Temporary interruption of treatment is recommended in patients undergoing major surgical procedure to prevent interference with wound healing. Hand-foot skin reaction (HFSR) or palmar-plantar erythrodysesthesia syndrome and rash represent the most frequently observed dermatological adverse reactions with regorafenib. Dose reduction and/or temporary interruption of regorafenib, or in severe or persistent cases, permanent discontinuation of regorafenib should be considered. Increased incidence of electrolyte abnormalities (including hypophosphatemia, hypocalcaemia, hyponatraemia and hypokalaemia) and metabolic abnormalities (including increases in thyroid stimulating hormone, lipase and amylase) has been associated with treatment. **Interactions:** Inducers of metabolic enzymes (e.g. CYP3A4 inducers such as rifampicin), decrease regorafenib concentrations. Inhibitors of metabolic enzymes (e.g. CYP3A4 inhibitor, such as ketoconazole), increase regorafenib concentrations. *In vitro* data indicates that regorafenib inhibits glucuronidation mediated by UGT1A1 and UGT1A9 and co-administration of regorafenib may increase systemic exposure to UGT1A1 and UGT1A9 substrates. Co-administration of regorafenib may increase the plasma concentrations of other concomitant Breast cancer resistance protein (BCRP) substrates (e.g. methotrexate, fluvastatin, atorvastatin). Recommend to monitor patients closely for signs and symptoms of increased exposure to BCRP substrates. Regorafenib inhibited CYP2C8, CYP2C9 and CYP2B6. The *in vitro* inhibitory potency towards CYP3A4 and CYP2C19 was less pronounced. Pharmacokinetic data indicate that concomitant administration of regorafenib with substrates of CYP2C8, CYP2C9, CYP3A4, and CYP2C19 did not result in clinically meaningful drug interactions. Co-administration of antibiotics that affect the flora of the gastrointestinal tract may interfere with the enterohepatic circulation of regorafenib and may result in decreased regorafenib exposure. Forms insoluble complexes with bile salt-sequestering agents (e.g. cholestyramine and cholestagel). **Fertility, pregnancy & lactation:** Fertility: Results from animal studies indicate that regorafenib can impair male and female fertility. Women of child-bearing potential must be informed that regorafenib may cause foetal harm. Both women of childbearing potential and men should ensure effective contraception during treatment and up to 8 weeks after completion of therapy. Pregnancy: No data on use in pregnant women. Animal studies have shown reproductive toxicity. Women of childbearing potential need to be informed that regorafenib can cause foetal harm. Regorafenib should not be used during pregnancy unless clearly necessary; risk to foetus should be considered. Lactation: Breast-feeding must be discontinued during treatment with regorafenib. **Effects on ability to drive and use machines:** No studies have been performed; if patients experience symptoms affecting their ability to concentrate and react during treatment, it is recommended not to drive or use machines until the effect subsides. **Undesirable effects:** The most serious adverse reactions were severe liver injury*, haemorrhage* and gastrointestinal perforation and infection*. *Very common*: infection*, thrombocytopenia, anaemia, decreased appetite and food intake, haemorrhage*, hypertension, dysphonia, diarrhoea, stomatitis, vomiting, nausea, constipation, hyperbilirubinaemia, increase in transaminases, HFSR (palmar-plantar erythrodysesthesia syndrome), rash, asthenia/fatigue, pain**, fever, mucosal inflammation, weight loss. *Common:* leucopenia, hypothyroidism, hypokalaemia, hypophosphataemia, hypocalcaemia, hyponatraemia, hypomagnesaemia, hyperuricaemia, dehydration, headache, tremor, peripheral neuropathy, taste disorders, dry mouth, gastro-oesophageal reflux, gastroenteritis, alopecia, dry skin, exfoliative rash, muscle spasms, proteinuria, increase in amylase, increase in lipase abnormal international normalised ratio. *Serious: cf. CI/W&P* - in addition: hypersensitivity reaction, myocardial infarction or ischaemia, gastrointestinal perforation* or fistula, pancreatitis, severe liver injury*, hypertensive crisis, nail disorder, erythema multiforme, squamous cell carcinoma of the skin. Posterior reversible encephalopathy syndrome (PRES), Stevens-Johnson syndrome, toxic epidermal necrolysis, aneurysms and artery dissections. Prescribers should consult the SmPC in relation to other side effects. *fatal cases have been reported. ** Most frequently reported types of pain (≥10%) are abdominal pain and back pain **Special Precautions for Storage:** Store in the original package in order to protect from moisture. Keep the bottle tightly closed and keep the desiccant in the bottle. **Legal Category:** POM. **Package Quantities & Basic NHS Costs:** Pack of 84 (3 bottles of 28) tablets, £3744.00. **MA Number(s):** EU/1/13/858/002, PLGB 00010/0702 **Further information available from:** Bayer plc, 400 South Oak Way, Reading, RG2 6AD United Kingdom. Telephone: 0118 206 3000. **Date of preparation:** March 2023 Stivarga® is a trademark of the Bayer Group

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk or search for MHRA YellowCard in Google Play or Apple App Store. Adverse events should also be reported to Bayer plc.
Tel: 0118 206 3500, Fax: 0118 206 3703,
Email: pvuk@bayer.com