ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Stivarga 40 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 40 mg of regorafenib.

Excipients with known effect:
Each daily dose of 160 mg contains 2.427 mmol (or 55.8 mg) of sodium (see section 4.4).
Each daily dose of 160 mg contains 1.68 mg of lecithin (derived from soya) (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Light pink film-coated tablets, oval shaped with a length of 16 mm and a width of 7 mm marked with 'BAYER' on one side and '40' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Stivarga is indicated for the treatment of adult patients with

- 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 therapy (see section 5.1).

- unresectable or metastatic gastrointestinal stromal tumors (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.

4.2 Posology and method of administration

Stivarga should be prescribed by physicians experienced in the administration of anticancer therapy.

Posology
The recommended dose of regorafenib is 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.

If a dose is missed, then it should be taken on the same day as soon as the patient remembers. The patient should not take two doses on the same day to make up for a missed dose. 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 (see section 4.4).

Patients with performance status (PS) 2 or higher were excluded from clinical studies. There is limited data in patients with PS ≥2.

Posology adjustments
Dose interruptions and/or dose reductions may be required based on individual safety and tolerability. Dose modifications are to be applied in 40 mg (one tablet) steps. The lowest recommended daily dose is 80 mg. The maximum daily dose is 160 mg.

For recommended dose modifications and measures in case of hand-foot skin reaction (HFSR) / palmar-plantar erythrodysesthesia syndrome see Table 1.

Table 1: Recommended dose modifications and measures for HFSR

Skin toxicity grade	Occurrence	Recommended dose modification and measures
Grade 1	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief.
Grade 2	1st occurrence	Decrease dose by 40 mg (one tablet) and immediately institute supportive measures. If no improvement occurs despite dose reduction, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1. A dose re-escalation is permitted at the discretion of the physician.
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.
	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.
	4th occurrence	Discontinue treatment with Stivarga permanently.
Grade 3	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40 mg (one tablet).
	3rd occurrence	Discontinue treatment with Stivarga permanently.

For recommended measures and dose modifications in case of worsening of liver function tests considered related to treatment with Stivarga see Table 2 (see also section 4.4).

Table 2: Recommended measures and dose modifications in case of drug-related liver function test abnormalities

Observed elevations of ALT and/or AST	Occurrence	Recommended measures and dose modification
≤5 times upper limit of normal (ULN) (maximum Grade 2)	Any occurrence	Continue Stivarga treatment. Monitor liver function weekly until transaminases return to <3 times ULN (Grade 1) or baseline.
>5 times ULN ≤20 times ULN (Grade 3)	1st occurrence	Interrupt Stivarga treatment. Monitor transaminases weekly until return to <3 times ULN or baseline. Restart: If the potential benefit outweighs the risk of hepatotoxicity, re-start Stivarga treatment, reduce dose by 40 mg (one tablet), and monitor liver function weekly for at least 4 weeks.
	Re-occurrence	Discontinue treatment with Stivarga permanently.
>20 times ULN (Grade 4)	Any occurrence	Discontinue treatment with Stivarga permanently.
>3 times ULN (Grade 2 or higher) with concurrent bilirubin >2 times ULN	Any occurrence	Discontinue treatment with Stivarga permanently. Monitor liver function weekly until resolution or return to baseline. Exception: patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST.

Hepatic impairment
Regorafenib is eliminated mainly via the hepatic route.
In clinical studies, no relevant differences in exposure, safety or efficacy were observed between patients with mild hepatic impairment (Child-Pugh A) and normal hepatic function. No dose adjustment is required in patients with mild hepatic impairment. Since only limited data are available for patients with moderate hepatic impairment (Child Pugh B), no dose recommendation can be provided. Close monitoring of overall safety is recommended in these patients (see sections 4.4 and 5.2).

Stivarga is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) as Stivarga has not been studied in this population.

Renal impairment
In clinical studies, no relevant differences in exposure, safety or efficacy were observed between patients with mild renal impairment (estimated Glomerular Filtration Rate [eGFR] 60-89 mL/min/1.73m^2) and patients with normal renal function. Limited pharmacokinetic data indicate no difference in exposure in patients with moderate renal impairment (eGFR 30-59 mL/min/1.73m^2). No dose adjustment is required in patients with mild or moderate renal impairment (see also section 5.2). No clinical data are available in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2).

Elderly population
In clinical studies, no relevant differences in exposure, safety or efficacy were observed between elderly (aged 65 years and above) and younger patients (see also section 5.2).

Gender
In clinical studies, no relevant differences in exposure, safety or efficacy were observed between male and female patients. No dose adjustment is necessary based on gender (see also section 5.2).

Ethnic differences
In clinical studies, no relevant differences in exposure or efficacy were observed between patients of different ethnic groups. A higher incidence of hand foot skin reaction (HFSR) / palmar-plantar erythrodysesthesia syndrome, severe liver function test abnormalities and hepatic dysfunction was observed in Asian (in particular Japanese) patients treated with Stivarga compared with Caucasians. The Asian patients treated with Stivarga in clinical studies were primarily from East Asia (~90%). There is limited data on regorafenib in the black patient population.
No dose adjustment is necessary based on ethnicity (see section 5.2).

Paediatric population
There is no relevant use of Stivarga in the paediatric population in the indication of metastatic colorectal cancer.
The safety and efficacy of regorafenib in patients below 18 years of age in the indication gastrointestinal stromal tumors (GIST) have not been established. No data are available.

Method of administration
Stivarga is for oral use.

Stivarga should be taken at the same time each day. The tablets should be swallowed 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).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hepatic effects
Abnormalities of liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST] and bilirubin) have been frequently observed in patients treated with Stivarga. Severe liver function test abnormalities (Grade 3 to 4) and hepatic dysfunction with clinical manifestations (including fatal outcomes) have been reported in a small proportion of patients (see section 4.8).
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 (see section 4.2).

It is recommended to perform liver function tests (ALT, AST and bilirubin) before initiation of treatment with Stivarga and monitor closely (at least every two weeks) during the first 2 months of treatment. Thereafter, periodic monitoring should be continued at least monthly and as clinically indicated.

Regorafenib is a uridine diphosphate glucuronosyl transferase (UGT) 1A1 inhibitor (see section 4.5). Mild, indirect (unconjugated) hyperbilirubinaemia may occur in patients with Gilbert's syndrome.

For patients with observed worsening of liver function tests considered related to treatment with Stivarga (i.e. where no alternative cause is evident, such as post-hepatic cholestasis or disease

progression), the dose modification and monitoring advice in Table 2 should be followed (see section 4.2).

Regorafenib is eliminated mainly via the hepatic route.
Close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment (see also sections 4.2 and 5.2). Stivarga is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) as Stivarga has not been studied in this population and exposure might be increased in these patients.

Haemorrhage
Stivarga has been associated with an increased incidence of haemorrhagic events, some of which were fatal (see section 4.8). 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. In the event of severe bleeding necessitating urgent medical intervention, permanent discontinuation of Stivarga should be considered.

Cardiac ischaemia and infarction
Stivarga has been associated with an increased incidence of myocardial ischaemia and infarction (see section 4.8). Patients with unstable angina or new onset angina (within 3 months of starting Stivarga therapy), recent myocardial infarction (within 6 months of starting Stivarga therapy) and those with cardiac failure New York Heart Association (NYHA) Classification 2 or higher were excluded from the clinical studies.

Patients with a history of ischaemic heart disease should be monitored for clinical signs and symptoms of myocardial ischaemia. In patients who develop cardiac ischaemia and/or infarction, interruption of Stivarga is recommended until resolution. The decision to re-start Stivarga therapy should be based on careful consideration of the potential benefits and risks of the individual patient. Stivarga should be permanently discontinued if there is no resolution.

Posterior reversible encephalopathy syndrome (PRES)
PRES has been reported in association with Stivarga treatment (see section 4.8). Signs and symptoms of PRES include seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging. In patients developing PRES, discontinuation of Stivarga, along with control of hypertension and supportive medical management of other symptoms is recommended.

Gastrointestinal perforation and fistula
Gastrointestinal perforation (including fatal outcome) and fistulae have been reported in patients treated with Stivarga (see section 4.8). These events are also known to be common disease-related complications in patients with intra-abdominal malignancies. Discontinuation of Stivarga is recommended in patients developing gastrointestinal perforation or fistula.

Arterial hypertension
Stivarga has been associated with an increased incidence of arterial hypertension (see section 4.8). Blood pressure should be controlled prior to initiation of treatment with Stivarga. It is recommended to monitor blood pressure and to treat hypertension in accordance with standard medical practice. In cases of severe or persistent hypertension despite adequate medical management, treatment should be temporarily interrupted and/or the dose reduced at the discretion of the physician (see section 4.2). In case of hypertensive crisis, Stivarga should be discontinued.

Wound healing complications
As medicinal products with anti-angiogenic properties may suppress or interfere with wound healing, temporary interruption of Stivarga is recommended for precautionary reasons in patients undergoing

major surgical procedures. The decision to resume treatment with Stivarga following major surgical intervention should be based on clinical judgment of adequate wound healing.

Dermatological toxicity
Hand-foot skin reaction (HFSR) or palmar-plantar erythrodysesthesia syndrome and rash represent the most frequently observed dermatological adverse reactions with Stivarga (see section 4.8). In clinical trials, a higher incidence of HFSR was observed in Asian (in particular Japanese) patients treated with Stivarga as compared with Caucasians (see section 4.2). Measures for the prevention of HFSR include control of calluses and use of shoe cushions and gloves to prevent pressure stress to soles and palms. Management of HFSR may include the use of keratolytic creams (e.g. urea-, salicylic acid-, or alpha hydroxyl acid-based creams applied sparingly only on affected areas) and moisturizing creams (applied liberally) for symptomatic relief. Dose reduction and/or temporary interruption of Stivarga, or in severe or persistent cases, permanent discontinuation of Stivarga should be considered (see section 4.2).

Biochemical and metabolic laboratory test abnormalities
Stivarga has been associated with an increased incidence of electrolyte abnormalities (including hypophosphatemia, hypocalcaemia, hyponatraemia and hypokalaemia) and metabolic abnormalities (including increases in thyroid stimulating hormone, lipase and amylase). The abnormalities are generally of mild to moderate severity, not associated with clinical manifestations, and do not usually require dose interruptions or reductions. It is recommended to monitor biochemical and metabolic parameters during Stivarga treatment and to institute appropriate replacement therapy according to standard clinical practice if required. Dose interruption or reduction, or permanent discontinuation of Stivarga should be considered in case of persistent or recurrent significant abnormalities (see section 4.2).

Important information about some of the ingredients
Each daily dose of 160 mg contains 2.427 mmol (or 55.8 mg) of sodium. To be taken into consideration by patients on a controlled sodium diet. Each daily dose of 160 mg contains 1.68 mg of lecithin (derived from soya).

4.5 Interaction with other medicinal products and other forms of interaction

Inhibitors of CYP3A4 and UGT1A9 / inducers of CYP3A4
In vitro data indicate that regorafenib is metabolized by cytochrome CYP3A4 and uridine diphosphate glucuronosyl transferase UGT1A9.

Administration of ketoconazole (400 mg for 18 days), a strong CYP3A4 inhibitor, with a single dose of regorafenib (160 mg on day 5) resulted in an increase in mean exposure (AUC) of regorafenib of approximately 33%, and a decrease in mean exposure of the active metabolites, M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl), of approximately 90%. It is recommended to avoid concomitant use of strong inhibitors of CYP3A4 activity (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin and voriconazole) as their influence on the steady-state exposure of regorafenib and its metabolites has not been studied.

Co-administration of a strong UGT1A9 inhibitor (e.g. mefenamic acid, diflunisal, and niflumic acid) during regorafenib treatment should be avoided, as their influence on the steady-state exposure of regorafenib and its metabolites has not been studied.

Administration of rifampicin (600 mg for 9 days), a strong CYP3A4 inducer, with a single dose of regorafenib (160 mg on day 7) resulted in a reduction in AUC of regorafenib of approximately 50%, a 3- to 4-fold increase in mean exposure of the active metabolite M-5, and no change in exposure of active metabolite M-2. Other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital and St. John's wort) may also increase metabolism of regorafenib. Strong inducers of CYP3A4 should

be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered.

UGT1A1 and UGT1A9 substrates

In vitro data indicate that regorafenib as well as its active metabolite M-2 inhibit glucuronidation mediated by UGT1A1 and UGT1A9 whereas M-5 only inhibits UGT1A1 at concentrations which are achieved *in vivo* at steady state. Administration of regorafenib with a 5-day break prior to administration of irinotecan resulted in an increase of approximately 44% in AUC of SN-38, a substrate of UGT1A1 and an active metabolite of irinotecan. An increase in AUC of irinotecan of approximately 28% was also observed. This indicates that co-administration of regorafenib may increase systemic exposure to UGT1A1 and UGT1A9 substrates.

Breast cancer resistance protein (BCRP) and P-glycoprotein substrates

Administration of regorafenib (160 mg for 14 days) prior to administration of a single dose of rosuvastatin (5 mg), a BCRP substrate, resulted in a 3.8-fold increase in mean exposure (AUC) of rosuvastatin and a 4.6-fold increase in C_{max}.

This indicates that co-administration of regorafenib may increase the plasma concentrations of other concomitant BCRP substrates (e.g. methotrexate, fluvastatin, atorvastatin). Therefore, it is recommended to monitor patients closely for signs and symptoms of increased exposure to BCRP substrates.

Clinical data indicate that regorafenib has no effect on digoxin pharmacokinetics, therefore can be given concomitantly with p-glycoprotein substrates, such as digoxin, without a clinically meaningful drug interaction.

Inhibitors of P-glycoprotein and BCRP / Inducers of P-glycoprotein and BCRP

In vitro studies indicate that the active metabolites M-2 and M-5 are substrates for P-glycoprotein and BCRP. Inhibitors and inducers of BCRP and P-glycoprotein may interfere with the exposure of M-2 and M-5. The clinical significance of these findings is unknown.

CYP isoform-selective substrates

In vitro data indicate that regorafenib is a competitive inhibitor of the cytochromes CYP2C8 (K_i value of 0.6 micromolar), CYP2C9 (K_i value of 4.7 micromolar), CYP2B6 (K_i value of 5.2 micromolar) at concentrations which are achieved *in vivo* at steady state (peak plasma concentration of 8.1 micromolar). The *in vitro* inhibitory potency towards CYP3A4 (K_i value of 11.1 micromolar) and CYP2C19 (K_i value of 16.4 micromolar) was less pronounced.

A clinical probe substrate study was performed to evaluate the effect of 14 days of dosing with 160 mg regorafenib on the pharmacokinetics of probe substrates of CYP2C8 (rosiglitazone) CYP2C9 (S-warfarin), CYP 2C19 (omeprazole) and CYP3A4 (midazolam).

Pharmacokinetic data indicate that regorafenib may be given concomitantly with substrates of CYP2C8, CYP2C9, CYP3A4, and CYP2C19 without a clinically meaningful drug interaction (see also section 4.4).

Antibiotics

The concentration-time profile indicates that regorafenib and its metabolites may undergo enterohepatic circulation (see section 5.2). Co-administration with neomycin, a poorly absorbed antimicrobial agent used for eradicating the gastrointestinal microflora (which may interfere with the enterohepatic circulation of regorafenib) had no effect on the regorafenib exposure, but there was an approximately 80% decrease in the exposure of the active metabolites M-2 and M-5 which showed *in vitro* and *in vivo* comparable pharmacological activity as regorafenib. The clinical significance of this

neomycin interaction is unknown, but may result in a decreased efficacy of regorafenib. Pharmacokinetic interactions of other antibiotics have not been studied.

Bile salt-sequestering agents
Regorafenib, M-2 and M-5 are likely to undergo enterohepatic circulation (see section 5.2). Bile salt-sequestering agents such as cholestyramine and cholestagel may interact with regorafenib by forming insoluble complexes which may impact absorption (or reabsorption), thus resulting in potentially decreased exposure. The clinical significance of these potential interactions is unknown, but may result in a decreased efficacy of regorafenib.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
Women of childbearing potential must be informed that regorafenib may cause foetal harm.
Women of childbearing potential and men should ensure effective contraception during treatment and up to 8 weeks after completion of therapy.

Pregnancy
There are no data on the use of regorafenib in pregnant women.
Based on its mechanism of action regorafenib is suspected to cause foetal harm when administered during pregnancy. Animal studies have shown reproductive toxicity (see section 5.3).
Stivarga should not be used during pregnancy unless clearly necessary and after careful consideration of the benefits for the mother and the risk to the foetus.

Breast-feeding
It is unknown whether regorafenib or its metabolites are excreted in human milk.
In rats, regorafenib or its metabolites are excreted in milk. A risk to the breast-fed child cannot be excluded. Regorafenib could harm infant growth and development (see section 5.3).
Breast-feeding must be discontinued during treatment with Stivarga.

Fertility
There are no data on the effect of Stivarga on human fertility. Results from animal studies indicate that regorafenib can impair male and female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects of Stivarga on the ability to drive or use machines have been performed. If patients experience symptoms affecting their ability to concentrate and react during treatment with Stivarga, it is recommended that they do not drive or use machines until the effect subsides.

4.8 Undesirable effects

Summary of the safety profile
The overall safety profile of Stivarga is based on data from more than 1,200 treated patients in clinical trials including placebo-controlled phase III data for 500 patients with metastatic colorectal cancer (CRC) and 132 patients with gastrointestinal stromal tumours (GIST).

The safety profile of regorafenib in these studies was consistent with the safety results of a phase III B study conducted in 2872 patients with metastatic colorectal cancer whose disease had progressed after treatment with standard therapies.

The **most serious** adverse drug reactions in patients receiving Stivarga are severe liver injury, haemorrhage and gastrointestinal perforation.

The **most frequently** observed adverse drug reactions (≥30%) in patients receiving Stivarga are asthenia/fatigue, hand foot skin reaction, diarrhoea, decreased appetite and food intake, hypertension, dysphonia and infection.

Tabulated list of adverse reactions
The adverse drug reactions reported in clinical trials in patients treated with Stivarga are shown in Table 3. They are classified according to System Organ Class and the most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.
Adverse drug reactions are grouped according to their frequencies. Frequency groups are defined by the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); and rare (≥1/10,000 to <1/1,000).

Within each frequency group, undesirable effects are presented in order of decreasing seriousness.

Table 3: Adverse drug reactions (ADRs) reported in clinical trials in patients treated with Stivarga

System Organ Class (MedDRA)	Very common	Common	Uncommon	Rare
Infections and infestations	Infection			
Neoplasms benign, malignant and unspecified (including cysts and polyps)				Keratoacanthoma/ Squamous cell carcinoma of the skin
Blood and lymphatic system disorders	Thrombocytopenia Anaemia	Leucopenia		
Immune system disorders			Hypersensitivity reaction	
Endocrine disorders		Hypothyroidism		
Metabolism and nutrition disorders	Decreased appetite and food intake	Hypokalaemia Hypophosphatemia Hypocalcaemia Hyponatraemia Hypomagnesaemia Hyperuricaemia		
Nervous system disorders	Headache	Tremor		Posterior reversible encephalopathy syndrome (PRES)
Cardiac disorders			Myocardial infarction Myocardial ischaemia	
Vascular disorders	Haemorrhage* Hypertension		Hypertensive crisis	

System Organ Class (MedDRA)	Very common	Common	Uncommon	Rare
Respiratory, thoracic and mediastinal disorders	Dysphonia			
Gastrointestinal disorders	Diarrhoea Stomatitis Vomiting Nausea	Taste disorders Dry mouth Gastro-oesophagea l reflux Gastroenteritis	Gastrointestinal perforation* Gastrointestinal fistula	
Hepatobiliary disorders	Hyperbilirubin-aemia	Increase in transaminases	Severe liver injury*#	
Skin and subcutaneous tissue disorders	Hand-foot skin reaction** Rash Alopecia	Dry skin Exfoliative rash	Nail disorder Erythema multiforme	Stevens-Johnson syndrome Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders		Musculoskeletal stiffness		
Renal and urinary disorders		Proteinuria		
General disorders and administration site conditions	Asthenia/fatigue Pain Fever Mucosal inflammation			
Investigations	Weight loss	Increase in amylase Increase in lipase Abnormal International normalised ratio		

* fatal cases have been reported
** palmar-plantar erythrodysesthesia syndrome in MedDRA terminology
# according to drug-induced liver injury (DILI) criteria of the international DILI expert working group

Description of selected adverse reactions

In most cases of severe liver injury, liver dysfunction had an onset within the first 2 months of therapy, and was characterized by a hepatocellular pattern of injury with transaminase elevations >20xULN, followed by bilirubin increase. In clinical trials, a higher incidence of severe liver injury with fatal outcome was observed in Japanese patients (~1.5%) treated with Stivarga compared with non-Japanese patients (<0.1%).

In the two placebo-controlled phase III trials, the overall incidence of hemorrhage was 19.3% in patients treated with Stivarga. Most cases of bleeding events in patients treated with Stivarga were mild to moderate in severity (Grades 1 and 2: 16.9%), most notably epistaxis (7.6%). Fatal events in patients treated with Stivarga were uncommon (0.6%), and involved the respiratory, gastrointestinal and genitourinary tracts.

In the two placebo-controlled phase III trials, infections were more often observed in patients treated with Stivarga as compared to patients receiving placebo (all grades: 31.0% vs. 14.4%). Most infections in patients treated with Stivarga were mild to moderate in severity (Grades 1 and 2: 22.9%), and

included urinary tract infections (6.8%), nasopharyngitis (4.2%) as well as mucocutaneous and systemic fungal infections (2.4%). No difference in fatal outcomes associated with infection between treatment groups was observed (0.6%, Stivarga arm vs. 0.6%, placebo arm)

In the placebo-controlled metastatic CRC phase III trial, the overall incidence of hand-foot skin reaction was 45.2% in patients treated with Stivarga as compared to 7.1% in patients receiving placebo. In the placebo-controlled GIST phase III trial, the overall incidence of hand-foot skin reaction was 66.7% in patients treated with Stivarga as compared to 15.2% in patients receiving placebo. In both trials, most cases of hand-foot skin reaction in patients treated with Stivarga appeared during the first cycle of treatment and were mild to moderate in severity (Grades 1 and 2: 28.6%, CRC and 44.7%, GIST). The incidence of Grade 3 hand-foot skin reaction was 16.6% (CRC) and 22.0% (GIST). In both trials, the overall incidence of hand-foot skin reaction (78.4%, CRC and 88.2%, GIST) was higher in Stivarga-treated Asian patients compared to other ethnicities. The incidence of Grade 3 hand-foot skin reaction in Asians was 28.4% (CRC) and 23.5% (GIST) (see sections 4.2 and 4.4).

In the placebo-controlled metastatic CRC phase III trial the overall incidence of hypertension was 30.4% in patients treated with Stivarga as compared to 7.9% in patients receiving placebo. In the placebo-controlled GIST phase III trial, the overall incidence of hypertension was 59.1% in patients treated with Stivarga as compared to 27.3% in patients receiving placebo. In both trials, most cases of hypertension in patients treated with Stivarga appeared during the first cycle of treatment and were mild to moderate in severity (Grades 1 and 2: 22.8%, CRC and 31.1%, GIST). The incidence of Grade 3 hypertension was 7.6% (CRC) and 27.3% (GIST). One case of Grade 4 hypertension was reported in the GIST trial.

In the placebo-controlled phase III trial in patients with metastatic CRC, the overall incidence of treatment emergent proteinuria was 7.4% in patients treated with Stivarga as compared to 2.4% in patients receiving placebo. Of these events, 40.5% in the Stivarga arm and 66.7% in the placebo arm have been reported as not recovered / not resolved. In the placebo-controlled GIST phase III trial, the overall incidence of proteinuria was 6.8% in patients treated with Stivarga compared to 1.5% in patients receiving placebo.

Across all clinical trials, cardiac disorder events (all grades) have been more often (20.5% vs. 10.4%) reported in Stivarga-treated patients aged 75 years or older (N=78) as compared to Stivarga-treated patients below 75 years (N=995).

<u>Laboratory test abnormalities</u>
Treatment-emergent laboratory abnormalities observed in the placebo-controlled phase III trials are shown in Table 4, 4a and Table 5 (see also section 4.4).

Table 4: Treatment-emergent laboratory test abnormalities reported in placebo-controlled phase III trial in patients with metastatic CRC (CORRECT)

Laboratory parameter (in % of samples investigated)	Stivarga plus BSC§ (N=500)			Placebo plus BSC§ (N=253)		
	All Grades*	Grade 3*	Grade 4*	All Grades*	Grade 3*	Grade 4*
Blood and lymphatic system disorders						
Haemoglobin decreased	78.5	4.7	0.6	66.3	2.8	0
Platelet count decreased	40.5	2.4	0.4	16.8	0.4	0
Neutrophil count decreased	2.8	0.6	0	0	0	0
Lymphocyte count decreased	54.1	9.3	0	34.4	3.2	0
Metabolism and nutrition disorders						
Calcium decreased	59.3	1.0	0.2	18.3	1.2	0
Potassium decreased	25.7	4.3	0	8.3	0.4	0
Phosphate decreased	57.4	30.5	0.6	11.1	3.6	0
Hepatobiliary disorders						
Bilirubin increased	44.6	9.6	2.6	17.1	5.2	3.2
AST increased	65.0	5.3	0.6	45.6	4.4	0.8
ALT increased	45.2	4.9	0.6	29.8	2.8	0.4
Renal and urinary disorders						
Proteinuria	59.7	0.4	0	34.1	0.4	0
Investigations						
INR increased**	23.7	4.2	-#	16.6	1.6	-#
Lipase increased	46.0	9.4	2.0	18.7	2.8	1.6
Amylase increased	25.5	2.2	0.4	16.7	2.0	0.4

§ Best Supportive Care
* Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
** International normalized ratio
# No Grade 4 denoted in CTCAE, Version 3.0

Compared to the global phase III CRC trial (CORRECT) with predominantly (~80%) Caucasian patients enrolled, a higher incidence of liver enzyme increases was observed in Stivarga-treated patients in the Asian phase III CRC trial (CONCUR) with predominantly (> 90%) East Asian patients enrolled.

Table 4a: Treatment emergent liver enzyme test abnormalities reported in placebo-controlled phase III trial in Asian patients with metastatic CRC (CONCUR)

Laboratory parameter, (in % of samples investigated)	Stivarga plus BSC§ (N=136)			Placebo plus BSC§ (N=68)		
	All Grades*	Grade 3*	Grade 4*	All Grades*	Grade 3*	Grade 4*
Bilirubin increased	66.7	7.4	4.4	32.8	4.5	0.0
AST increased	69.6	10.4	0.7	47.8	3.0	0.0
ALT increased	54.1	8.9	0.0	29.9	1.5	0.0

§ Best Supportive Care
* Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0

Table 5: Treatment-emergent laboratory test abnormalities reported in placebo-controlled phase III trial (double-blind phase) in patients with GIST (GRID)

Laboratory parameter, (in % of samples investigated)	Stivarga plus BSC§ (N=132)			Placebo plus BSC§ (N=66)		
	All Grades*	Grade 3*	Grade 4*	All Grades*	Grade 3*	Grade 4*
Blood and lymphatic system disorders						
Haemoglobin decreased	75.0	3.0	0	72.7	1.5	0
Platelet count decreased	12.9	0.8	0	1.5	0	1.5
Neutrophil count decreased	15.9	2.3	0	12.1	3.0	0
Lymphocyte count decreased	29.5	7.6	0	24.2	3.0	0
Metabolism and nutrition disorders						
Calcium decreased	16.7	1.5	0	4.5	0	0
Potassium decreased	20.5	3.0	0	3.0	0	0
Phosphate decreased	54.5	19.7	1.5	3.1	1.5	0
Hepatobiliary disorders						
Bilirubin increased	33.3	3.0	0.8	12.1	1.5	0
AST increased	58.3	3.0	0.8	47.0	3.0	0
ALT increased	39.4	3.8	0.8	39.4	1.5	0
Renal and urinary disorders						
Proteinuria	38.5	1.5	-	39.0	1.7	-
Investigations						
INR increased**	9.3	1.6	-	12.5	4.7	-
Lipase increased	14.4	0	0.8	4.6	0	0

§ Best Supportive Care
* Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0
** International normalized ratio
- No Grade 4 denoted in CTCAE, Version 4.0

In the two placebo-controlled phase III trials, tests on thyroid stimulating hormone (TSH) showed post baseline >ULN in 26.1% of patients treated with Stivarga and in 15.1% of patients receiving placebo. TSH post baseline >4 times ULN was reported in 6.9% of patients treated with Stivarga and in 0.7% of patients receiving placebo. Concentration of free triiodothyronine (FT3) post baseline below lower limit of normal (<LLN) was reported in 25.6% of patients treated with Stivarga and in 20.9% of patients receiving placebo. Concentration of free thyroxin (FT4) post baseline <LLN was reported in 8.0% of patients treated with Stivarga and 6.6% of patients receiving placebo. Overall approximately 7% of patients treated with Stivarga developed hypothyroidism requiring hormonal replacement treatment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The highest dose of Stivarga studied clinically was 220 mg per day. The most frequently observed adverse drug reactions at this dose were dermatological events, dysphonia, diarrhoea, mucosal inflammation, dry mouth, decreased appetite, hypertension, and fatigue.

There is no specific antidote for Stivarga overdose. In the event of suspected overdose, Stivarga should be discontinued immediately, with best supportive care initiated by a medical professional, and the patient should be observed until clinical stabilisation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitor;
ATC Code: L01XE21

Mechanism of action and pharmacodynamic effects
Regorafenib is an oral tumour deactivation agent that potently blocks multiple protein kinases, including kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, $BRAF^{V600E}$), and the tumour microenvironment (PDGFR, FGFR). In particular, regorafenib inhibits mutated KIT, a major oncogenic driver in gastrointestinal stromal tumors, and thereby blocks tumor cell proliferation. In preclinical studies regorafenib has demonstrated potent antitumour activity in a broad spectrum of tumour models including colorectal and gastrointestinal stromal tumour models which is mediated by its anti-angiogenic and anti-proliferative effects. In addition, regorafenib has shown anti-metastatic effects *in vivo*. Major human metabolites (M-2 and M-5) exhibited similar efficacies compared to regorafenib in *in vitro* and *in vivo* models.

Clinical efficacy and safety

Metastatic colorectal cancer (CRC)

The clinical efficacy and safety of Stivarga have been evaluated in an international, multi-centre, randomised, double-blind, placebo-controlled phase III study (CORRECT) in patients with metastatic colorectal cancer who have progressed after failure of standard therapy.

The primary efficacy endpoint was Overall Survival (OS). Secondary endpoints were Progression-Free Survival (PFS), objective tumour response rate and disease control rate.

In total, 760 patients were randomised 2:1 to receive 160 mg regorafenib (4 tablets Stivarga each containing 40 mg regorafenib) orally once daily (N=505) plus Best Supportive Care (BSC) or matching placebo (N=255) plus BSC for 3 weeks on therapy followed by 1 week off therapy. The mean daily regorafenib dose received was 147 mg.

Patients continued therapy until disease progression or unacceptable toxicity. A pre-planned interim analysis for efficacy was performed when 432 deaths had occurred. The study was un-blinded after this planned interim analysis of OS had crossed the pre-specified efficacy boundary.

Of the 760 randomised patients, the median age was 61 years, 61% were male, 78% were Caucasian, and all patients had baseline ECOG Performance Status (PS) of 0 or 1. PS ≥2 was reported during Stivarga treatment in 11.4% of patients. The median treatment duration and daily dose, as well as the rate of dose modification and dose reduction were similar to those observed in patients with a reported PS ≥ 2 receiving placebo (8.3%). The majority of patients with PS ≥2 discontinued treatment for progressive disease. The primary site of disease was colon (65%), rectum (29%), or both (6%). A KRAS mutation was reported in 57% of patients at study entry.

Most patients (52%) received 3 or fewer previous lines of treatment for metastatic disease. Therapies included treatment with fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if the patient was KRAS wild type, an anti-EGFR therapy.

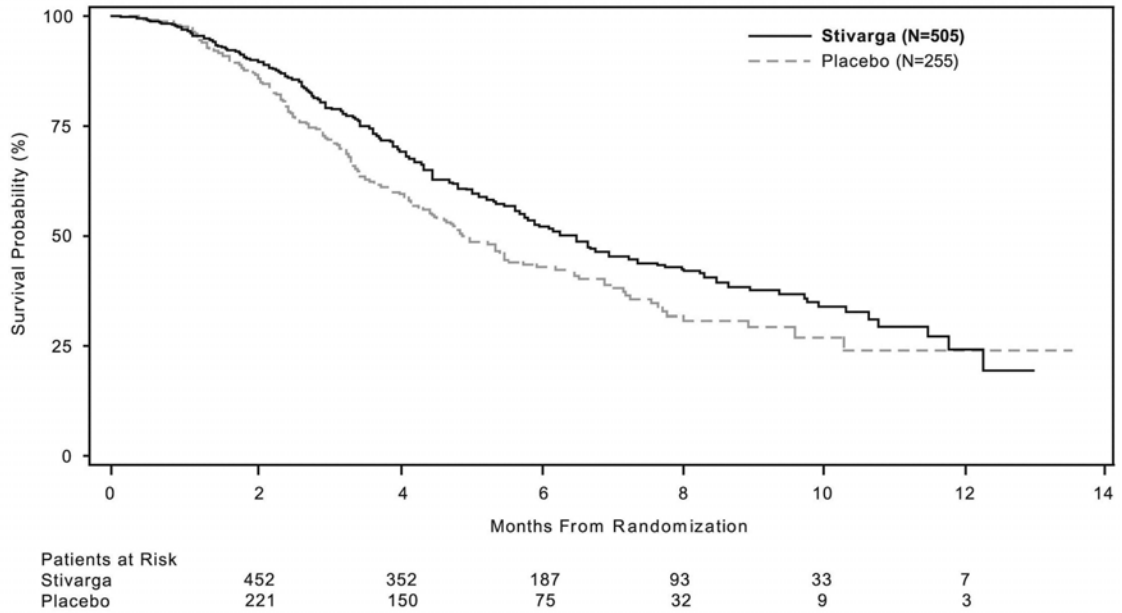
The addition of Stivarga to BSC resulted in significantly longer survival as compared to placebo plus BSC with a hazard ratio of 0.774 (p=0.005178 stratified log rank test) and a median OS of 6.4 months vs. 5.0 months [95% CI 0.636, 0.942] (see Table 6 and Figure 1). PFS was significantly longer in patients receiving Stivarga plus BSC (hazard ratio: 0.494, p<0.000001, see Table 6). The response rate (complete response or partial response) was 1% and 0.4% for Stivarga and placebo treated patients, respectively (p=0.188432, 1-sided). The disease control rate (complete response or partial response or stable disease) was significantly higher in patients treated with Stivarga (41.0% vs. 14.9%, p<0.000001, 1 sided).

Table 6: Efficacy results from the CORRECT study

Efficacy parameter	Hazard ratio* (95% CI)	P-value (one-sided)	Median (95% CI)	
			Stivarga plus BSC§ (N=505)	Placebo plus BSC§ (N=255)
Overall Survival	0.774 (0.636, 0.942)	0.005178	6.4 months (5.9, 7.3)	5.0 months (4.4, 5.8)
Progression Free Survival**	0.494 (0.419, 0.582)	<0.000001	1.9 months (1.9, 2.1)	1.7 months (1.7, 1.7)

§ Best Supportive Care
* Hazard ratio < 1 favours Stivarga
** based on investigator's assessment of tumour response

Figure 1: Kaplan-Meier curve of overall survival



Subgroup analyses for overall survival and progression free survival according to age (<65; ≥65), gender, ECOG PS, primary site of disease, time from first diagnosis of metastatic disease, prior anticancer treatment, prior treatment lines for metastatic disease, and KRAS mutation showed a treatment effect favouring the regorafenib regimen over the placebo regimen.

Subgroup analysis results by historical KRAS mutational status showed a treatment effect for OS in favour of regorafenib over placebo for patients with KRAS wild-type tumours whereas a numerically lower effect was reported in patients with KRAS mutant tumours; the treatment effect for PFS favouring regorafenib was observed regardless of KRAS mutational status. The hazard ratio (95% CI) of overall survival was 0.653 (0.476 to 0.895) for patients with KRAS wild-type tumours and 0.867 (0.670 to 1.123) for patients with KRAS mutant tumours, with no evidence of heterogeneity in treatment effect (non-significant interaction test). The hazard ratio (95% CI) of progression free survival was 0.475 (0.362 to 0.623) for patients with KRAS wild-type tumours and 0.525 (0.425 to 0.649) for patients with KRAS mutant tumours.

A second phase III, international, multi-center, randomized, double blind, placebo-controlled study (CONCUR) evaluated the efficacy and safety of Stivarga in 204 pre-treated Asian patients (> 90% East Asian) with metastatic colorectal cancer who have progressed after failure of fluoropyrimidine-based chemotherapy. Only 59.5 % of patients enrolled in the CONCUR study were also previously treated with VEGF- or EGFR-targeted agents. The primary efficacy endpoint was OS. The addition of Stivarga to BSC resulted in a significantly longer survival, as compared to placebo plus BSC with a hazard ratio of 0.550 (p = 0.000159 stratified log rank test) and a median OS of 8.8 months vs. 6.3 months [95% CI 0.395, 0.765]. PFS was also significantly longer in patients receiving Stivarga plus BSC (hazard ratio: 0.311, p<0.000001), median PFS 3.2 months with Stivarga vs. 1.7 months with placebo. The safety profile of Stivarga plus BSC in the CONCUR study was consistent with the safety profile observed in the CORRECT study.

Gastrointestinal stromal tumours (GIST)

The clinical efficacy and safety of Stivarga have been evaluated in an international, multi-center, randomized, double-blind, placebo-controlled phase III study (GRID) in patients with gastrointestinal stromal tumors (GIST) previously treated with 2 tyrosine kinase inhibitors (imatinib and sunitinib).

The analysis of the primary efficacy endpoint Progression-Free Survival (PFS) was conducted after 144 PFS events (central blinded assessment). Secondary endpoints including Time To Progression (TTP) and Overall Survival (OS) (interim analysis) were also assessed.

In total, 199 patients with GIST were randomized 2:1 to receive either 160 mg regorafenib plus Best Supportive Care (BSC; N=133) orally once daily or matching placebo plus BSC (N=66) for 3 weeks on therapy followed by 1 week off therapy. The mean daily regorafenib dose received was 140 mg.

Patients continued therapy until disease progression or unacceptable toxicity. Patients receiving placebo who experienced disease progression were offered open-label regorafenib (cross-over option). Patients receiving regorafenib who experienced disease progression and for whom in the investigator's opinion, treatment with regorafenib was providing clinical benefit, were offered the opportunity to continue open-label regorafenib.

Of the 199 randomized patients, the mean age was 58 years, 64% were male, 68% were Caucasian, and all patients had baseline ECOG Performance Status (PS) of 0 or 1. The overall median time since most recent progression or relapse to randomization was 6 weeks.

Regorafenib plus BSC resulted in significantly longer PFS as compared to placebo plus BSC with a hazard ratio of 0.268 [95% CI 0.185, 0.388] and a median PFS of 4.8 months vs. 0.9 months ($p < 0.000001$). The relative risk of disease progression or death was reduced by approximately 73.2% in regorafenib-treated patients compared to placebo treated patients (see Table 7, Figure 2).The increase in PFS was consistent independent of age, sex, geographic region, prior lines of treatment, ECOG PS.

TTP was significantly longer in the patients receiving regorafenib plus BSC than in patients receiving placebo plus BSC with a hazard ratio of 0.248 [95% CI 0.170, 0.364], and median TTP of 5.4 months versus 0.9 months ($p<0.000001$) (see Table 7).

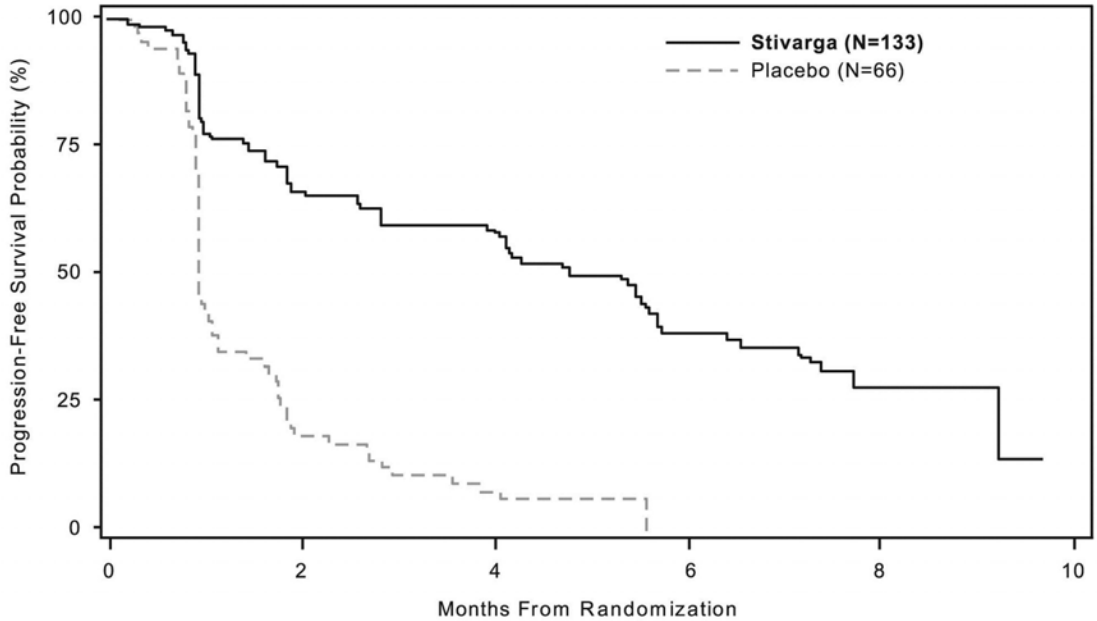
The HR for OS was 0.772 (95% CI, 0.423, 1.408; $p = 0.199$; median OS not reached in either arm); 85% of patients initially randomized to the placebo arm received post-progression treatment with regorafenib (see Table 7, Figure 3).

Table 7: Efficacy Results from the GRID study

Efficacy parameter	Hazard Ratio* (95% CI)	P-value (one-sided)	Median (95% CI)	
			Stivarga plus BSC§ (N=133)	Placebo plus BSC§ (N=66)
Progression-Free Survival	0.268 (0.185, 0.388)	<0.000001	4.8 months (4.0, 5.7)	0.9 months (0.9, 1.1)
Time To Progression	0.248 (0.170,0.364)	<0.000001	5.4 months (4.1, 5.7)	0.9 months (0.9, 1.1)
Overall Survival	0.772 (0.423, 1.408)	0.199	NR**	NR**

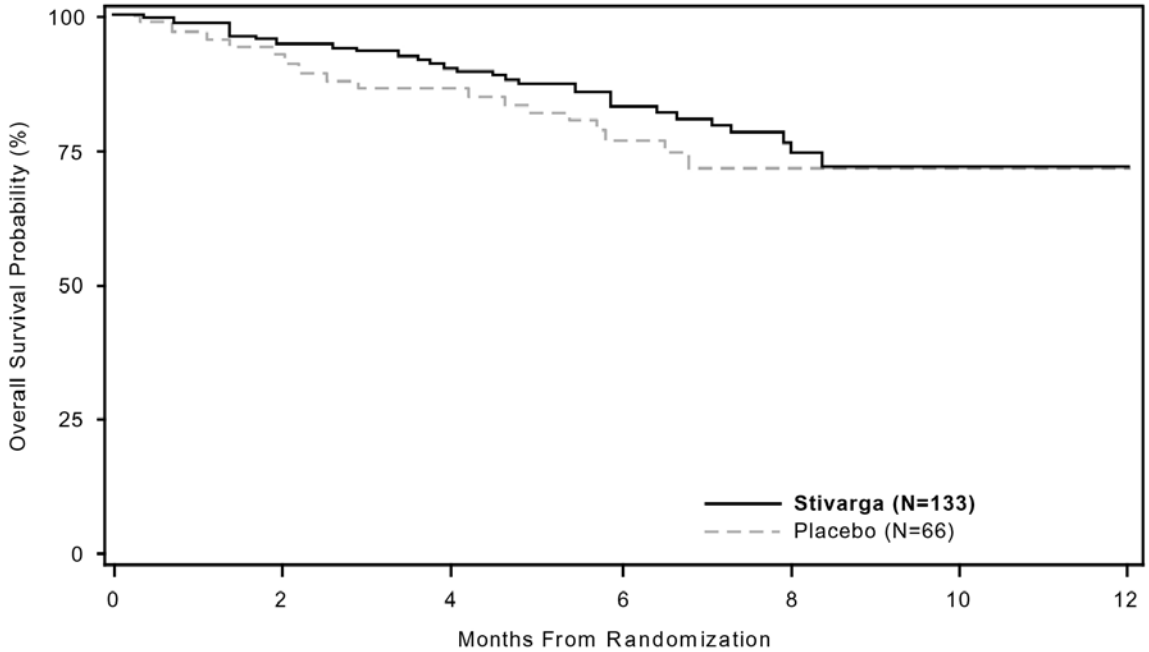
§ Best Supportive Care
* Hazard ratio < 1 favors Stivarga
** NR: not reached

Figure 2: Kaplan-Meier curves of Progression-Free Survival



Patients at Risk				
Stivarga	82	72	27	9
Placebo	12	5	0	0

Figure 3: Kaplan-Meier curves of Overall Survival



Patients at Risk						
Stivarga	126	119	94	39	10	1
Placebo	61	57	41	16	3	1

In addition, 56 placebo plus BSC patients received open-label Stivarga after cross-over following disease progression and a total of 41 Stivarga plus BSC patients continued Stivarga treatment after disease progression. The median secondary PFS (as measured by the investigator's assessment) were 5.0 and 4.5 months, respectively.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Stivarga in all subsets of the paediatric population in the treatment of adenocarcinoma of the colon and rectum (see section 4.2 for information on paediatric use).
The European Medicines Agency has deferred the obligation to submit the results of studies with Stivarga in one or more subsets of the paediatric population in the treatment of solid malignant tumours (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Regorafenib reaches mean peak plasma levels of about 2.5 mg/l at about 3 to 4 hours after a single oral dose of 160 mg given as 4 tablets each containing 40 mg. Following single doses of 60 mg or 100 mg, the average relative bioavailability of tablets compared to an oral solution was 69% and 83%, respectively.

The concentrations of regorafenib and its major pharmacologically active metabolites (M-2 and M-5) were highest when given after a low-fat (light) breakfast as compared to either a high-fat breakfast or fasting condition. The exposure for regorafenib was increased by 48% when administered with a high-fat breakfast, and 36% when administered with a low fat breakfast, compared to fasting. The exposure of metabolites M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl) is higher when regorafenib is given with a low fat breakfast as compared to fasting condition and lower when given with a high fat meal as compared to fasting condition.

Distribution
Plasma concentration-time profiles for regorafenib as well as for the major circulating metabolites showed multiple peaks across the 24-hour dosing interval, which are attributed to enterohepatic circulation. *In vitro* protein binding of regorafenib to human plasma proteins is high (99.5%). *In vitro* protein binding of M-2 and M-5 is higher (99.8% and 99.95%, respectively) than that of regorafenib. Metabolites M-2 and M-5 are weak substrates of P-gp. Metabolite M-5 is a weak BCRP-substrate.

Biotransformation
Regorafenib is metabolized primarily in the liver by oxidative metabolism mediated by CYP3A4, as well as by glucuronidation mediated by UGT1A9. Two major and six minor metabolites of regorafenib have been identified in plasma. The main circulating metabolites of regorafenib in human plasma are M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl), which are pharmacologically active and have similar concentrations as regorafenib at steady state. M-2 is further metabolised by oxidative metabolism mediated by CYP3A4, as well as by glucuronidation mediated by UGT1A9.

Metabolites may be reduced or hydrolysed in the gastrointestinal tract by microbial flora, allowing reabsorption of the unconjugated active substance and metabolites (enterohepatic circulation).

Elimination
Following oral administration, mean elimination half-life for regorafenib and its metabolite M-2 in plasma ranges from 20 to 30 hours in different studies. The mean elimination half-life for the metabolite M-5 is approximately 60 hours (range from 40 to 100 hours).
Approximately 90% of the radioactive dose was recovered within 12 days after administration, with about 71% of the dose excreted in faeces (47% as parent compound, 24% as metabolites), and about

19% of the dose excreted in urine as glucuronides. Urinary excretion of glucuronides decreased below 10% under steady-state conditions. Parent compound found in faeces could be derived from intestinal degradation of glucuronides or reduction of metabolite M-2 (N-oxide), as well as unabsorbed regorafenib.
M-5 may be reduced to M-4 in the gastrointestinal tract by microbial flora, allowing reabsorption of M-4 (enterohepatic circulation). M-5 is finally excreted via M-4 as M-6 (carboxylic acid) in faeces.

Linearity/non-linearity
Systemic exposure of regorafenib at steady-state increases dose proportionally up to 60 mg and less than proportionally at doses greater than 60 mg. Accumulation of regorafenib at steady state results in about a 2-fold increase in plasma concentrations, which is consistent with the elimination half-life and dosing frequency. At steady state, regorafenib reaches mean peak plasma levels of about 3.9 mg/L (8.1 micromolar) after oral administration of 160 mg regorafenib and the peak-to-trough ratio of mean plasma concentrations is less than 2.
Both metabolites, M-2 and M-5, exhibit non-linear accumulation, which might be caused by entero-hepatic recycling or saturation of the UGT1A9 pathway. Whereas plasma concentrations of M-2 and M-5 after a single dose of regorafenib are much lower than those of parent compound, steady-state plasma concentrations of M-2 and M-5 are comparable to those of regorafenib.

Hepatic impairment

The exposure of regorafenib and its metabolites M-2 and M-5 is comparable in patients with mild hepatic impairment (Child-Pugh A) and patients with normal hepatic function.
Limited data in patients with moderate hepatic impairment (Child-Pugh B) indicate similar exposure as compared to patients with normal hepatic function after a single 100 mg dose of regorafenib. There are no data for patients with Child-Pugh C (severe) hepatic impairment. Regorafenib is mainly eliminated via the liver, and exposure might be increased in this patient population.

Renal impairment
Available clinical data and physiology-based pharmacokinetic modelling indicate similar steady-state exposure of regorafenib and its metabolites M-2 and M-5 in patients with mild and moderate renal impairment compared to patients with normal renal function.
The pharmacokinetics of regorafenib has not been studied in patients with severe renal impairment or end-stage renal disease. However, physiology-based pharmacokinetic modelling does not predict any relevant change in exposure in these patients.

Elderly
Age did not affect the regorafenib pharmacokinetics over the studied age range (29 – 85 years).

Gender
The pharmacokinetics of regorafenib is not influenced by gender.

Ethnic differences
The exposure of regorafenib in various Asian populations (Chinese, Japanese, Korean) is within the same range as seen in Caucasians.

Cardiac electrophysiology/QT prolongation
No QTc prolonging effects were observed after administration of 160 mg regorafenib at steady state in a dedicated QT study in male and female cancer patients.

5.3 Preclinical safety data

Systemic toxicity
After repeated dosing to mice, rats and dogs, adverse effects were observed in a number of organs, primarily in the kidneys, liver, digestive tract, thyroid gland, lympho-/haematopoietic system, endocrine system, reproductive system and skin. A slightly increased incidence of thickening of the atrioventricular valves of the heart was seen in the 26 week repeat-dose toxicity study in rats. This may be due to acceleration of an age-related physiological process. These effects occurred at systemic exposures in the range of or below the anticipated human exposure (based on AUC comparison). Alterations of teeth and bones and adverse effects in the reproductive system were more pronounced in young and growing animals as well as in juvenile rats and indicate a potential risk for children and adolescents.

Reproductive and developmental toxicity
Specific studies on fertility have not been performed. However, a potential of regorafenib to adversely affect male and female reproduction has to be considered based on morphological changes in the testes, ovaries, and the uterus observed after repeated dosing in rats and dogs at exposures below the anticipated human exposure (based on AUC comparison). The observed changes were only partially reversible.

An effect of regorafenib on intrauterine development was shown in rabbits at exposures below the anticipated human exposure (based on AUC comparison). Main findings consisted of malformations of the urinary system, the heart and major vessels, and the skeleton.

Genotoxicity and carcinogenicity
There was no indication for a genotoxic potential of regorafenib tested in standard assays *in vitro* and *in vivo* in mice.

Studies on the carcinogenic potential of regorafenib have not been performed.

Environmental Risk Assessment (ERA)
Environmental risk assessment studies have shown that regorafenib has the potential to be persistent, bioaccumulative and toxic to the environment and may pose a risk to the surface water and to the sediment compartment (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose microcrystalline
Croscarmellose sodium
Magnesium stearate
Povidone (K-25)
Silica, colloidal anhydrous

Film coat
Iron oxide red (E172)
Iron oxide yellow (E172)
Lecithin (derived from soya)
Macrogol 3350
Polyvinyl alcohol, partially hydrolysed
Talc
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

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

6.4 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.

6.5 Nature and contents of container

White opaque HDPE bottle closed with a PP/PP (polypropylene) screw cap with sealing insert and a molecular sieve desiccant.

Each bottle contains 28 film-coated tablets.

Pack sizes
Pack of 28 film-coated tablets.
Pack of 84 (3 bottles of 28) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product may pose a risk to the environment (see section 5.3).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/858/001
EU/1/13/858/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Bayer Pharma AG

Kaiser-Wilhelm-Allee
51368 Leverkusen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal products subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
To submit pre-specified, exploratory genetic (including NRAS, KRAS, BRAF and PIK3CA) and non-genetic (ANG-2, IL-6, IL-8, P1GF, VEGFR-1, TIE1, VEGF-A, VEGF-C, VEGF-D, VEGF-A-121, BMP-7, VWF, M-CSF, SDF-1) appropriate biomarker analyses from study 15983 (randomised, double-blind, placebo-controlled phase-III study of adjuvant regorafenib versus placebo for patients with stage IV colorectal cancer after curative treatment of liver metastases). Genetic and non-genetic biomarker analysis should be implemented as mandatory for all enrolled patients.	31/12/2020

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Stivarga 40 mg film-coated tablets
regorafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 40 mg of regorafenib.

3. LIST OF EXCIPIENTS

Contains sodium and lecithin (derived from soya), see leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
84 (3 x 28) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. Keep the bottle tightly closed. Keep the desiccant in the bottle.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/858/001
EU/1/13/858/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

stivarga 40 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL

1. NAME OF THE MEDICINAL PRODUCT

Stivarga 40 mg film-coated tablets
regorafenib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 40 mg of regorafenib.

3. LIST OF EXCIPIENTS

Contains sodium and lecithin (derived from soya).

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. Keep the bottle tightly closed. Keep the desiccant in the bottle.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/858/001
EU/1/13/858/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Stivarga 40 mg film-coated tablets
regorafenib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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
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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 tumors (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).

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 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 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 or altered mental status** (such as confusion, memory loss or loss of orientation) please contact your doctor immediately

- **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 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 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 tumors (GIST) have not been established. No data are available.

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 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 2.427 mmol (or 55.8 mg) of **sodium** 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

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 or moderately impaired kidney function. There are no data available on the use of Stivarga in patients with a 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, bleeding and gastrointestinal perforation.

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.

Other side effects with Stivarga listed by frequency:

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

- infection
- 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
- headache
- 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*)
- redness, pain, blisters and swelling of the palms of the hands or soles of the feet (*hand-foot skin reaction*)
- rash
- hair loss (*alopecia)*
- weakness, lack of strength and energy, excessive tiredness and unusual sleepiness *(asthenia/fatigue)*
- pain
- 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, hypophosphataemia, hypocalcaemia, hyponatraemia and hypomagnesaemia*)
- high level of uric acid in the blood (*hyperuricaemia*)
- shaking (*tremor*)
- taste disorders
- dry mouth
- heartburn (*gastro-oesophageal reflux*)
- infection or irritation of the stomach and intestines (*gastroenteritis*)
- changes in enzymes produced by the liver, which may indicate that something is wrong with the liver (*increase in transaminases*)
- dry skin
- rash with flaking or peeling of skin *(exfoliative rash)*
- stiffness of the muscles or joints
- 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*)
- 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)**:**

- 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 leukoencephalopathy 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*).

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 national reporting system listed in Appendix V. 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 to protect it from moisture.

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

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).

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 of 28 tablets and in a pack comprising 3 bottles, each containing 28 tablets.

Not all pack sizes may be marketed.

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Bayer Pharma AG
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency (EMA) website: http://www.ema.europa.eu.