ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 2.438 mmol (or 56.06 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 as monotherapy 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 tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib

- hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

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
Available clinical data indicate similar exposure of regorafenib and its metabolites M-2 and M-5 in patients with mild, moderate or severe renal impairment compared to patients with normal renal function. No dose adjustment is required in patients with mild, moderate or severe renal impairment (see also section 5.2).

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 tumours (GIST) have not been established. No data are available.
There is no relevant use of Stivarga in the paediatric population in the indication of hepatocellular carcinoma.

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 hepatic failure and 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, 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.

Infections
Stivarga has been associated with an increased incidence of infection events, some of which were fatal (see section 4.8).
In cases of worsening infection events, interruption of Stivarga treatment should be considered.

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. Screening for and subsequent treatment of oesophageal varices in patients with liver cirrhosis should be performed as per standard of care before starting treatment with Stivarga. In the event of severe bleeding necessitating urgent medical intervention, permanent discontinuation of Stivarga should be considered.

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.

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.

Hyperammonaemic encephalopathy
Hyperammonaemic encephalopathy has been observed with regorafenib, including fatal cases (see section 4.8). In patients who develop unexplained lethargy or changes in mental status, ammonia levels should be measured and appropriate clinical management should be initiated. If hyperammonaemic encephalopathy is confirmed, permanent discontinuation of regorafenib should be considered.

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.

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.

Aneurysms and artery dissections
The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating Stivarga, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Thrombotic microangiopathy (TMA)
Thrombotic microangiopathy (TMA), including thrombotic thrombocytopaenic purpura (TTP), have been associated with the use of regorafenib (see section 4.8). The diagnosis of TMA should be considered in patients presenting with haemolytic anaemia, thrombocytopenia, fatigue, fluctuating neurological manifestation, renal impairment, and fever. Regorafenib therapy should be discontinued in patients who develop TMA and prompt treatment is required. Reversal of the effects of TMA has been observed after treatment discontinuation.

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, 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
This medicinal product contains 56.06 mg sodium per daily dose of 160 mg, equivalent to 3% of the WHO recommended maximum daily intake of 2 g sodium for an adult. 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 (see also section 5.2).

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 4,800 treated patients in clinical trials including placebo-controlled phase III data for 636 patients with metastatic colorectal cancer (CRC), 132 patients with gastrointestinal stromal tumours (GIST) and 374 patients with hepatocellular carcinoma (HCC).

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, gastrointestinal perforation and infection.

The **most frequently** observed adverse drug reactions (≥30%) in patients receiving Stivarga are pain, hand foot skin reaction, asthenia/fatigue, diarrhoea, decreased appetite and food intake, hypertension 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); rare (≥1/10,000 to <1/1,000) and not known (cannot be estimated from the available data).

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

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

System Organ Class (MedDRA)	Very common	Common	Uncommon	Rare	Not known
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		Thrombotic microangiopathy	
Immune system disorders			Hypersensitivity reaction		
Endocrine disorders		Hypothyroidism			
Metabolism and nutrition disorders	Decreased appetite and food intake	Hypokalaemia Hypophosphatemia Hypocalcaemia Hyponatraemia Hypomagnesaemia Hyperuricaemia Dehydration			
Nervous system disorders		Headache Tremor Peripheral neuropathy		Posterior reversible encephalopathy syndrome (PRES)	Hyperammonaemic encephalopathy
Cardiac disorders			Myocardial infarction Myocardial ischaemia		
Vascular disorders	Haemorrhage* Hypertension		Hypertensive crisis		Aneurysms and artery dissections

System Organ Class (MedDRA)	Very common	Common	Uncommon	Rare	Not known
Respiratory, thoracic and mediastinal disorders	Dysphonia				
Gastro-intestinal disorders	Diarrhoea Stomatitis Vomiting Nausea Constipation	Taste disorders Dry mouth Gastro-oesopha-geal reflux Gastro-enteritis	Gastro-intestinal perforation* Gastro-intestinal fistula Pancreatitis		
Hepatobiliary disorders	Hyper-bilirubinaemia Increase in transaminases		Severe liver injury (including hepatic failure)*[#]		
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	
Musculo-skeletal and connective tissue disorders		Muscle spasms			
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 Inter-national normalised ratio			

* fatal cases have been reported

** palmar-plantar erythrodysesthesia syndrome in MedDRA terminology

***Most frequently reported types of pain (≥10%) are abdominal pain and back pain

[#] 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 placebo-controlled phase III trials, the overall incidence of haemorrhage was 18.2% in patients treated with Stivarga and 9.5% in patients receiving placebo. Most cases of bleeding events in patients treated with Stivarga were mild to moderate in severity (Grades 1 and 2: 15.2%), most notably epistaxis (6.1%). Fatal outcome in patients treated with Stivarga was uncommon (0.7%), and included cerebral, respiratory, gastrointestinal and genitourinary events.

In the placebo-controlled phase III trials, infections were more often observed in patients treated with Stivarga, compared to patients receiving placebo (all grades: 31.6% vs. 17.2%). Most infections in patients treated with Stivarga were mild to moderate in severity (Grades 1 and 2: 23.0%), and included urinary tract infections (5.7%), nasopharyngitis (4.0%), mucocutaneous and systemic fungal infections (3.3%) as well as pneumonia (2.6%). Fatal outcomes associated with infection were observed more often in patients treated with Stivarga (1.0%), compared to patients receiving placebo (0.3%), and were mainly respiratory events.

In the placebo-controlled phase III trials, the overall incidence of hand-foot skin reaction was higher in patients treated with Stivarga, compared to patients receiving placebo (all grades: 51.4% vs. 6.5% CRC, 66.7% vs. 15.2% GIST and 51.6% vs.7.3% HCC). 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: 34.3%%, CRC, 44.7%, GIST and 39.3%, HCC). The incidence of Grade 3 hand-foot skin reaction was 17.1% (CRC), 22.0% (GIST) and 12.3% (HCC). The overall incidence of hand-foot skin reaction (74.8%, CRC, 88.2%, GIST and 67.1%, HCC) was higher in Stivarga-treated Asian patients, compared to other ethnicities. The incidence of Grade 3 hand-foot skin reaction in Asians was 20.5% (CRC), 23.5% (GIST) and 13.5% (HCC) (see sections 4.2 and 4.4).

In the placebo-controlled phase III trials, the overall incidence of hypertension was higher in patients treated with Stivarga, compared to patients receiving placebo (29.6% vs. 7.5% CRC, 60.6% vs. 25.8% GIST and 31.0% vs. 6.2% HCC). 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: 20.9%, CRC, 31.8%, GIST and 15.8% HCC). The incidence of Grade 3 hypertension was 8.7% (CRC), 28.0% (GIST) and 15.2% (HCC). One case of Grade 4 hypertension was reported in the GIST trial.

In the placebo-controlled phase III trials, the overall incidence of treatment emergent proteinuria was 9.1% in patients treated with Stivarga, compared to 1.9% in patients receiving placebo. Of these events, 35.6% in the Stivarga arm and 54.5% in the placebo arm have been reported as not recovered/not resolved.
Across all clinical trials, cardiac disorder events (all grades) have been more often (13.7% vs. 6.5%) reported in Stivarga-treated patients aged 75 years or older (N=410), compared to Stivarga-treated patients below 75 years (N=4108).

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

Table 4: Treatment-emergent laboratory test abnormalities reported in placebo-controlled phase III trials in patients with metastatic CRC (CORRECT), GIST (GRID) and HCC (RESORCE)

Laboratory Parameter (in % of samples investigated)	mCRC (CORRECT)				GIST (GRID)				HCC (RESORCE)			
	Stivarga plus BSC (n= 500)	Placebo plus BSC (n=253)	Stivarga plus BSC (n= 500)	Placebo plus BSC (n=253)	Stivarga plus BSC (n= 132)	Placebo plus BSC (n= 66)	Stivarga plus BSC (n=132)	Placebo plus BSC (n= 66)	Stivarga plus BSC (n= 374)	Placebo plus BSC (n=193)	Stivarga plus BSC (n= 374)	Placebo plus BSC (n=193)
	Grade [a]				Grade [b]				Grade [b]			
	All Grades %		Grade 3/4 %		All Grades %		Grade 3/4 %		All Grades %		Grade 3/4 %	
Blood and lymphatic system disorders												
Haemoglobin decreased	78.5	66.3	5.3	2.8	75.0	72.7	3.0	1.5	72.5	71.3	6.0	4.8
Thrombocytopenia	40.5	16.8	2.8	0.4	12.9	1.5	0.8	1.5	63.1	50.0	5.4	0
Neutropenia	2.8	0	0.6	0	15.9	12.1	3.1	3.0	13.6	14.9	3.0	1.0
Lymphopenia	54.1	34.8	9.3	4.0	29.9	24.2	7.6	3.0	67.8	58.5	17.4	11.7
Metabolism and nutrition disorders												
Hypocalcaemia	59.3	18.3	1.2	1.2	16.7	4.5	1.5	0	23.4	10.1	0.3	0
Hypokalemia	25.7	8.3	4.3	0.4	20.5	3.0	3.0	0	30.7	9.0	4.3	2.1
Hypophosphatemia	57.4	11.1	31.1	3.6	54.5	3.1	21.2	1.5	70.4	31.4	33.9	6.9
Hepatobiliary disorders												
Hyperbilirubinemia	44.6	17.1	12.2	8.4	33.3	12.1	3.8	1.5	78.2	54.5	15.9	15.7
Increased AST	65.0	45.6	5.9	5.2	58.3	47.0	3.8	3.0	92.7	84.3	17.8	19.9
Increased ALT	45.2	29.8	5.5	3.2	39.4	39.4	4.6	1.5	70.4	58.6	6.2	4.7
Renal and urinary disorders												
Proteinuria	83.6	61.0	1.8	0.8	59.2	52.5	3.1	3.4	51.0	36.5	16.7	3.1
Investigations												
Increased INR*	23.7	16.6	4.2	1.6	9.3	12.5	1.6	4.7	44.4	35.4	0.7	2.1
Increased Lipase	46.0	18.7	11.4	4.4	14.4	4.6	0.8	0	40.5	27.0	14.2	8.7
Increased Amylase	25.5	16.7	2.6	2.4	-	-	-	-	23.0	19.0	2.8	2.7

[a] Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0

[b] Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0

* International normalized ratio

BSC = Best Supportive Care

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

In the placebo-controlled phase III trials, tests on thyroid stimulating hormone (TSH) showed post baseline >ULN in 34.6% of patients treated with Stivarga and in 17.2% of patients receiving placebo. TSH post baseline >4 times ULN was reported in 6.5% of patients treated with Stivarga and in 1.3% of patients receiving placebo. Concentration of free triiodothyronine (FT3) post baseline below lower limit of normal (<LLN) was reported in 29.2% of patients treated with Stivarga and in 20.4% of patients receiving placebo. Concentration of free thyroxin (FT4) post baseline <LLN was reported in 8.1% of patients treated with Stivarga and 5.6% of patients receiving placebo. Overall approximately 4.6% 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:

United Arab Emirates (UAE): Emirates Drug Establishment Tel: 80033784 Email: pv@ede.gov.ae Website: www.ede.gov.ae	**Jordan:** Tel: +962-6-5632000 JFDA email : jpc@jfda.jo JFDA website: www.jfda.jo https://vigiflow-eforms.who-umc.org/jo/jpc
Kuwait: Drug &Food Control, Ministry of Health Tel.: +965-24811532 Fax: +965-24811507 Email : Adr_reporting@moh.gov.kw Website: http://eservices.moh.gov.kw/SPCMS/DrugCmp.aspx	**Oman:** Department of Pharmacovigilance & Drug Information Drug Safety Center - Ministry of Health Tel : +968 - 22357687 / 22357690 Fax : +968 - 22358489 Email: pharma-vigil@moh.gov.om Website: www.moh.gov.om
Egypt: Egyptian Pharmaceutical Vigilance Centre Hotline: 15301 Email: pv.followup@edaegypt.gov.eg Website: https://vigiflow-eforms.who-umc.org/eg/med	**Other Countries:** Please contact the relevant competent authority

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: L01EX05

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, $BRAF^{V600E}$), metastasis (VEGFR3, PDGFR, FGFR) and tumour immunity (CSF1R). In particular, regorafenib inhibits mutated KIT, a major oncogenic driver in gastrointestinal stromal tumours, and thereby blocks tumour cell proliferation. In preclinical studies regorafenib has demonstrated potent antitumour activity in a broad spectrum of tumour models including colorectal, gastrointestinal stromal and hepatocellular tumour models which is likely mediated by its anti-angiogenic and anti-proliferative effects. In addition, regorafenib reduced the levels of tumour associated macrophages and 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 (ORR) and Disease Control Rate (DCR).

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 $\geq$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 $\geq$ 2 receiving placebo (8.3%). The majority of patients with PS $\geq$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.

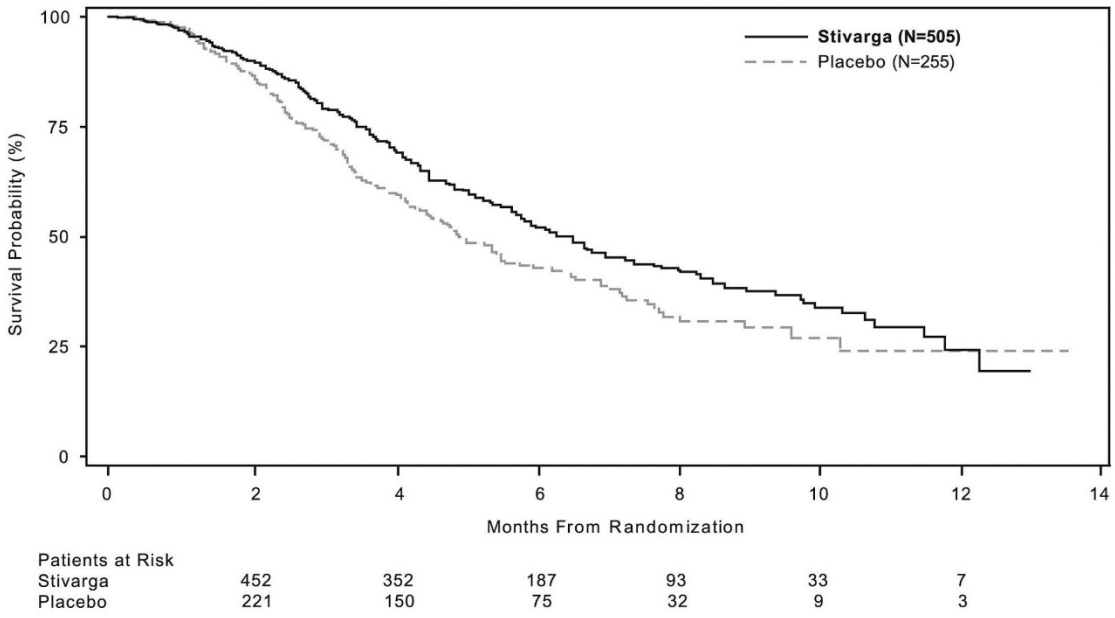
The addition of Stivarga to BSC resulted in significantly longer survival, compared to placebo plus BSC with a p value of 0.005178 from stratified log rank test, a hazard ratio of 0.774 [95% CI 0.636, 0.942]) and a median OS of 6.4 months vs. 5.0 months (see Table 5 and Figure 1). PFS was significantly longer in patients receiving Stivarga plus BSC (hazard ratio: 0.494, p<0.000001, see Table 5). 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 DCR (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 5: 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)
OS	0.774 (0.636, 0.942)	0.005178	6.4 months (5.9, 7.3)	5.0 months (4.4, 5.8)
PFS**	0.494 (0.419, 0.582)	<0.000001	1.9 months (1.9, 2.1)	1.7 months (1.7, 1.7)

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

Figure 1: Kaplan-Meier curve of OS



Subgroup analyses for OS and PFS 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 status 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 OS 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 PFS 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-centre, randomised, 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, 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-centre, randomised, double-blind, placebo-controlled phase III study (GRID) in patients with gastrointestinal stromal tumours (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 randomised 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 randomised 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 randomisation was 6 weeks.

Regorafenib plus BSC resulted in significantly longer PFS, 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 6, 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 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 vs. 0.9 months ($p<0.000001$) (see Table 6).

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 randomised to the placebo arm received post-progression treatment with regorafenib (see Table 6, Figure 3).

Table 6: 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)
PFS	0.268 (0.185, 0.388)	<0.000001	4.8 months (4.0, 5.7)	0.9 months (0.9, 1.1)
TTP	0.248 (0.170,0.364)	<0.000001	5.4 months (4.1, 5.7)	0.9 months (0.9, 1.1)
OS	0.772 (0.423, 1.408)	0.199	NR**	NR**

[§] Best Supportive Care
* Hazard ratio < 1 favours Stivarga
** NR: not reached

Figure 2: Kaplan-Meier curves of PFS

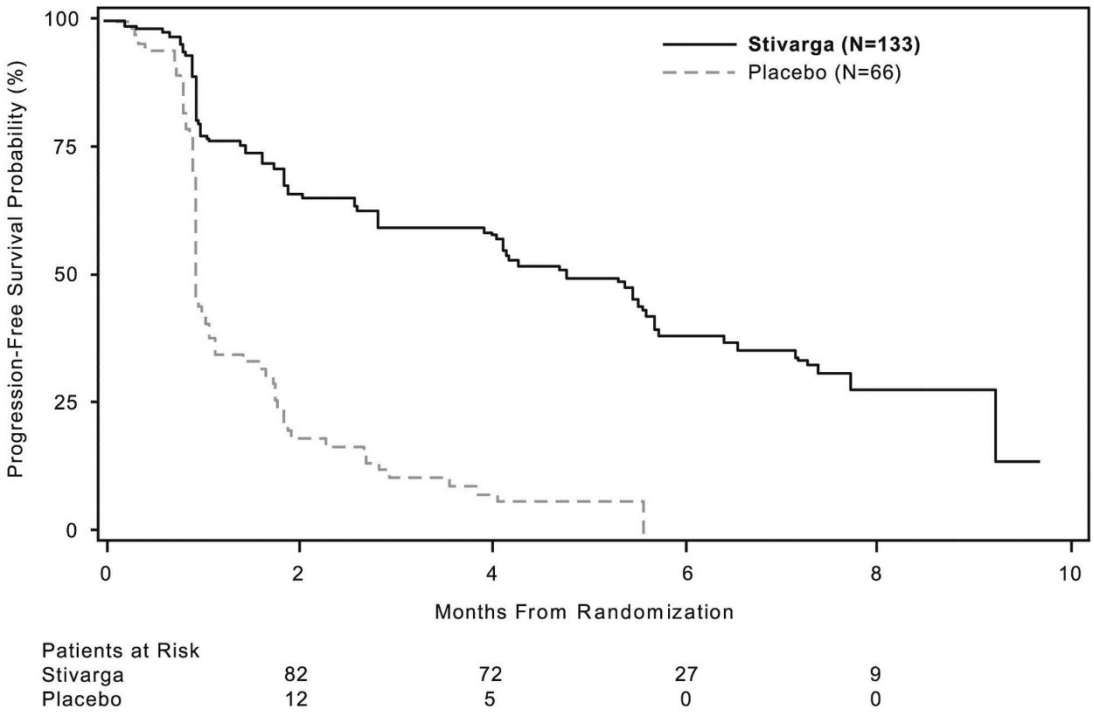
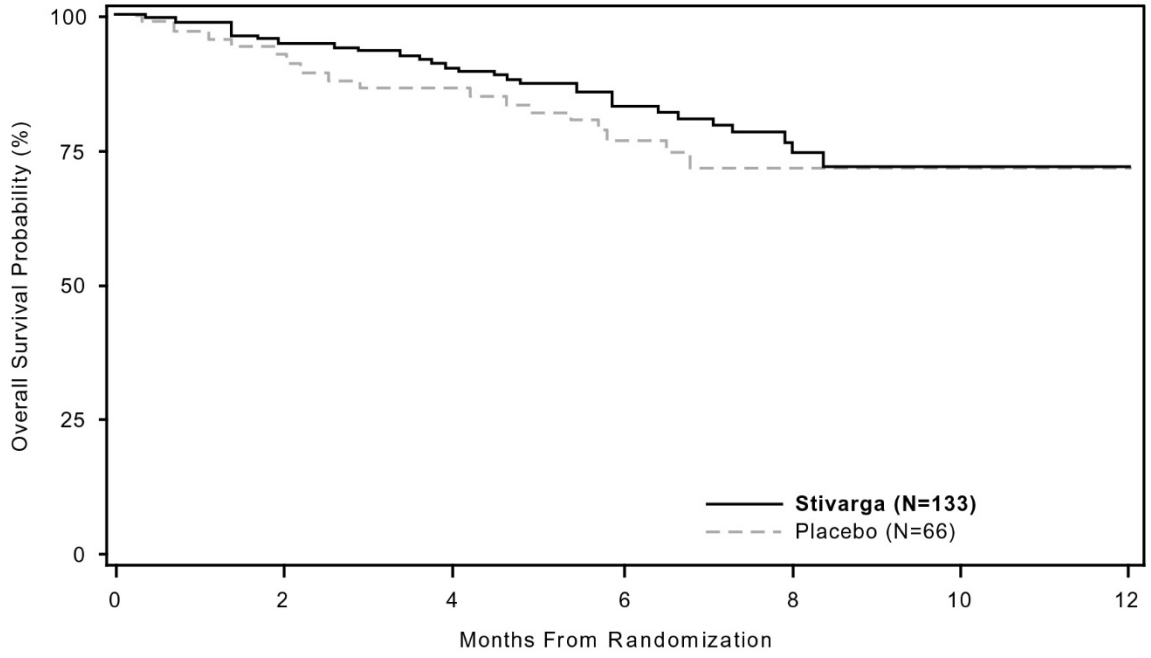


Figure 3: Kaplan-Meier curves of OS



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.

Hepatocellular carcinoma (HCC)

The clinical efficacy and safety of Stivarga have been evaluated in an international, multi-centre, randomised, double-blind, placebo-controlled phase III study (RESORCE) in patients with hepatocellular carcinoma who have been previously treated with sorafenib.

The primary efficacy endpoint was Overall Survival (OS). Secondary endpoints were Progression-Free Survival (PFS), Time To Progression (TTP), Objective Tumour Response Rate (ORR) and Disease Control Rate (DCR).

In total, 573 patients with HCC were randomised 2:1 to receive either 160 mg regorafenib orally once daily (n=379) plus Best Supportive Care (BSC) or matching placebo (n=194) plus BSC for 3 weeks on therapy followed by 1 week off therapy. The mean daily regorafenib dose received was 144 mg. Patients were eligible to participate in the study if they experienced radiological disease progression during treatment with sorafenib and if they had a liver function status of Child-Pugh class A. Patients who permanently discontinued sorafenib therapy due to sorafenib-related toxicity or who tolerated less than 400 mg sorafenib once daily prior to withdrawal were excluded from the study. Randomisation was performed within 10 weeks after the last treatment with sorafenib. Patients continued therapy with Stivarga until clinical or radiological disease progression or unacceptable toxicity. However, patients could continue Stivarga therapy past progression at the discretion of the investigator.

Demographics and baseline disease characteristics were comparable between the Stivarga- and placebo-treated groups and are shown below for all 573 randomised patients:

- Median age: 63 years
- Male: 88%

- Caucasian: 36%, Asian: 41%
- ECOG Performance Status (PS) of 0: 66% or ECOG PS of 1: 34%
- Child-Pugh A: 98%, Child-Pugh B: 2%
- Aetiology included Hepatitis B (38%), Hepatitis C (21%), Non-Alcoholic Steato Hepatitis (NASH, 7%)
- Absence of both macroscopic vascular invasion and extra-hepatic tumour spread: 19%
- Barcelona Clinic Liver Cancer (BCLC) stage B: 13%; BCLC stage C: 87%
- Loco-regional transarterial embolisation or chemoinfusion procedures: 61%
- Radiotherapy prior to regorafenib treatment: 15%
- Median duration of sorafenib treatment: 7.8 months

The addition of Stivarga to BSC resulted in a statistically significant improvement in OS compared to placebo plus BSC with a hazard ratio of 0.624 [95% CI 0.498, 0.782], p=0.000017 stratified log rank test, and a median OS of 10.6 months vs. 7.8 months (see Table 7 and Figure 4).

Table 7: Efficacy results from the RESORCE study

Efficacy parameter	**Hazard ratio* (95% CI)**	**P-value (one-sided)**	**Median (95% CI)**	
			Stivarga plus BSC§ (N=379)	**Placebo plus BSC§ (N=194)**
OS	0.624 (0.498,0.782)	0.000017	10.6 months (9.1, 12.1)	7.8 months (6.3, 8.8)
PFS**	0.453 (0.369, 0.555)	<0.000001	3.1 months (2.8, 4.2)	1.5 months (1.4, 1.6)
TTP**	0.439 (0.355,0.542)	<0.000001	3.2 months (2.9, 4.2)	1.5 months (1.4, 1.6)
			Percentages	
ORR**#	NA	0.003650	11%	4%
DCR **#	NA	<0.000001	65%	36%

§ Best Supportive Care
* Hazard ratio < 1 favours Stivarga
** based on investigator's assessment of tumour response by modified RECIST
# Response rate (complete or partial response), DCR (complete response, partial response and stable disease maintained for 6 weeks)

Figure 4: Kaplan-Meier curve of OS

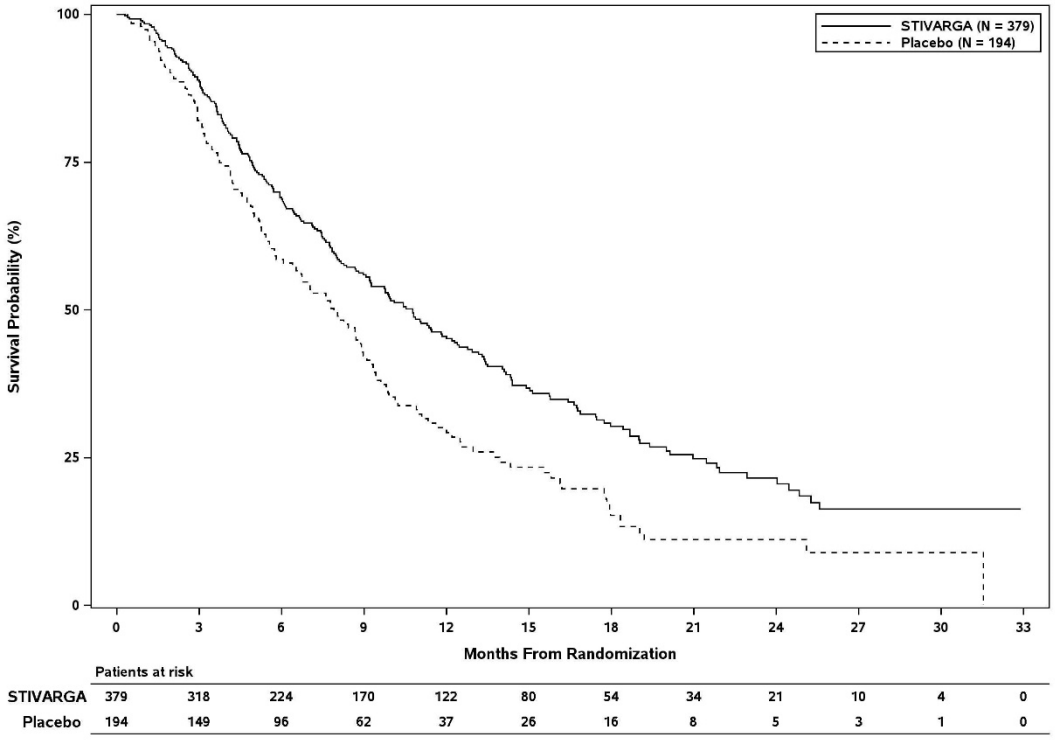
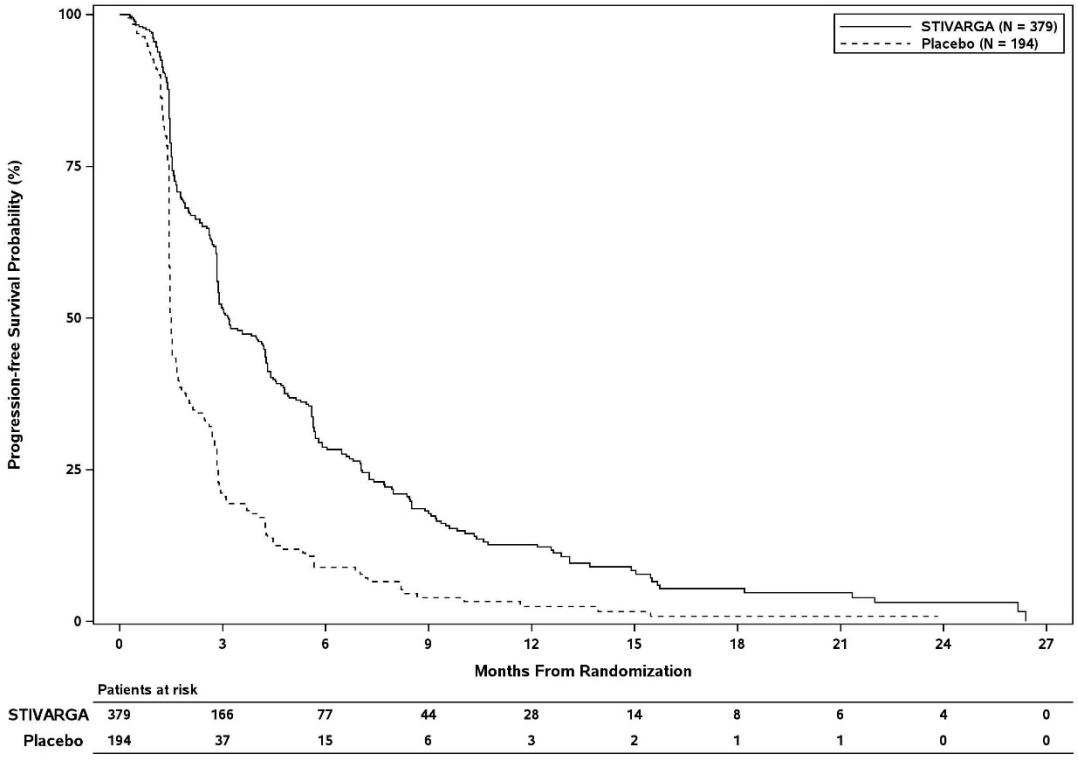


Figure 5: Kaplan-Meier curve of PFS (mRECIST)



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).
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 hepatocellular carcinoma (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, 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, compared to fasting condition and lower when given with a high fat meal, 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, 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 or moderate renal impairment, compared to patients with normal renal function. In patients with severe renal impairment compared to patients with normal renal function, regorafenib exposure was similar while exposure to M-2 and M-5 was decreased by about 30% under steady-state conditions, which is not considered clinically relevant.
The pharmacokinetics of regorafenib has not been studied in patients with 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.
Do not store above 30°C.

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

Keep the desiccant in the bottle.

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 AG
51368 Leverkusen
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
Date of latest renewal: 22 May 2018

10. DATE OF REVISION OF THE TEXT

06/2025