PROFESSIONAL INFORMATION

SCHEDULING STATUS
S4

1 NAME OF THE MEDICINE

STIVARGA® 40 mg
Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 40, 0 mg regorafenib.
Sugar free
Excipients with known effect
Each daily dose of 160 mg contains 2.4.27 mmol (or 55.8 mg) of sodium.
Each daily dose of 160 mg contains 1.68 mg of lecithin (derived from soya).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets
Light pink film-coated tablets, oval, 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 patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if RAS wild type, an anti-EGFR therapy.

- STIVARGA is indicated for the treatment of patients with gastrointestinal stromal tumours (GIST) who have been previously treated with 2 tyrosine kinase inhibitors.

- STIVARGA is indicated for the treatment of patients with hepatocellular carcinoma (HCC) progressing on one other appropriate systemic therapy.

4.2 Posology and method of administration

Posology
The recommended dose is 160 mg STIVARGA (4 tablets of STIVARGA each containing 40 mg regorafenib), taken orally once daily for 3 weeks on therapy followed by 1 week off therapy to comprise a cycle of 4 weeks.

If a dose of STIVARGA 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.

Treatment should continue as long as benefit is observed or until unacceptable toxicity occurs (see section 4.4).

Dose modification

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

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 treating medical practitioner
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0 - 1. When resuming treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the treating medical practitioner
	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0 - 1. When resuming treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the treating medical practitioner
	4th occurrence	Discontinue treatment.
Grade 3	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0 - 1. When resuming treatment, decrease dose by 40 mg (one tablet). A dose re-escalation is permitted at the discretion of the treating medical practitioner
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0 - 1. When resuming treatment, decrease dose by 40 mg (one tablet).
	3rd occurrence	Discontinue treatment.

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

Table 2: Recommended measures and dose modifications in case of STIVARGA-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 to ≤ 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-initiate 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.
No clinically important differences in exposure were observed between patients with mild (Child-Pugh A) or moderate hepatic impairment (Child Pugh B) compared to patients with normal hepatic function. No dose adjustment is required in patients with mild or moderate hepatic impairment.

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).

Ethnic differences:
In clinical studies, no relevant differences in exposure or efficacy were observed between patients of different ethnic groups. No dose adjustment is necessary based on ethnicity. A higher incidence of hand foot skin reaction (HFSR), severe liver function test abnormalities and hepatic dysfunction was observed in Asian (in particular Japanese) patients treated with STIVARGA as compared with Caucasians. The Asian patients treated with STIVARGA in clinical studies were primarily from East Asia (~90%).

Method of administration

STIVARGA is for oral use.

STIVARGA should be taken at the same time each day after a light meal. The tablets should be swallowed whole.

4.3 Contraindications

- Hypersensitivity to regorafenib or any of the other ingredients of STIVARGA.
- STIVARGA must not be used by pregnant women or by women who are breastfeeding their infants (see section 4.6).
- Patients who develop gastrointestinal perforations or fistula while taking STIVARGA should permanently discontinue treatment with STIVARGA

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 very commonly 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 (see section 4.8).

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 UGT1A1 inhibitor (see section 4.5). Indirect (unconjugated) hyperbilirubinemia 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 the Table 2 must be followed (see section 4.5).

Close monitoring of overall safety is recommended in patients with mild or moderate hepatic impairment (see sections 4.2 and 4.3). 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 or other concomitant medications that increase the risk of bleeding. 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 outcomes) and fistulae have been reported in patients treated with STIVARGA (see section 4.8). STIVARGA should be discontinued in patients developing gastrointestinal perforation or fistula (see section 4.3).

Cardiac ischaemia and infarction

STIVARGA has been associated with an increased incidence of myocardial ischaemia and infarction (see section 4.8).

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-initiate 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.
No difference between STIVARGA and placebo was observed in the incidence of clinically relevant cardiac dysrhythmias or heart failure.

Reversible posterior leukoencephalopathy syndrome

Reversible posterior leukoencephalopathy syndrome (RPLS) has been reported in association with STIVARGA treatment (see section 4.8). Signs and symptoms of RPLS include seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without associated hypertension. A diagnosis of RPLS requires confirmation by brain imaging. In patients developing RPLS, discontinuation of STIVARGA, along with control of hypertension and supportive medical management of other symptoms is recommended. The safety of re-initiating STIVARGA therapy in patients previously experiencing RPLS is not known.

Hyperammonemic encephalopathy

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

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, STIVARGA should be temporarily interrupted and/or the dose reduced at the discretion of the treating medical practitioner (see section 4.2 subsection “Dose modification”). In case of hypertensive crisis, STIVARGA should be discontinued.

Wound healing complications

No formal studies of the effect of STIVARGA on wound healing have been conducted. However, as medicines 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. There is limited clinical experience regarding the timing of re-initiation of therapy following major surgical intervention. Therefore, the decision to resume STIVARGA therapy following major surgical intervention should be based on clinical judgment of adequate wound healing.

Dermatological toxicity

Hand-foot skin reaction (HFSR/palmar-plantar erythrodysesthesia syndrome) and rash represent the most frequently observed dermatological adverse drug reactions with STIVARGA (see section 4.8). 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 moisturising 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 hypophosphataemia, hypocalcaemia, hyponatraemia and hypokalaemia) and metabolic abnormalities (including increases in thyroid stimulating hormone, lipase and amylase). These 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 ingredients

STIVARGA contains 55.8 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).

Disease-specific precautions – Hepatocellular carcinoma (HCC)

In the pivotal placebo-controlled phase III study, patients received prior therapy with sorafenib. There is insufficient data on patients who discontinued sorafenib therapy due to sorafenib-related toxicity or only tolerated a low dose (< 400 mg daily) of sorafenib. The tolerability of STIVARGA in these patients has not been established.

4.5 Interaction with other medicines and other forms of interaction

Inhibitors/inducers of CYP3A4

In vitro data indicate that regorafenib is metabolised by the cytochrome CYP3A4 and the 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 regorafenib exposure (AUC) of approximately 33 %, and a decrease in mean exposure to 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 (M-2 and M-5) has not been studied.

Administration of rifampin (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 mean regorafenib exposure (AUC) 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 inducers of CYP3A4 activity (e.g. phenytoin, carbamazepine, phenobarbitone and St. John's wort) may also increase metabolism of regorafenib. Since a reduction in plasma regorafenib concentrations may result in a decreased efficacy, strong inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicine, 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 inhibits glucuronidation mediated by uridine diphosphate glucuronosyl transferases 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) to SN-38, a substrate of UGT1A1 and an active metabolite of irinotecan. An increase in mean exposure to irinotecan of approximately 28 % was also observed. This indicates that co-administration of regorafenib may increase systemic exposure to UGT1A1 and UGT1A9 substrates. The clinical significance of these findings is unknown.

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 breast cancer resistance protein (BCRP) substrate, resulted in a 3.8-fold increase in mean exposure (AUC) of rosuvastatin and a 4.6-fold increase in Cmax.

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.

CYP isoform-selective substrates

In vitro data indicate that regorafenib is a competitive inhibitor of the cytochromes CYP2C8, CYP2C9, CYP2B6 at concentrations which are achieved *in vivo* at steady state (peak plasma concentration of 8,1 micromolar). The *in vitro* inhibitory potency towards CYP3A4 and CYP2C19 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).

4.6 Fertility, pregnancy and lactation

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

Pregnancy
STIVARGA is contraindicated in pregnancy (see section 4.3).
Based on its mechanism of action STIVARGA is suspected to cause foetal harm when administered during pregnancy. Animal studies have shown reproductive toxicity.

Breastfeeding
Breastfeeding must be discontinued during treatment with STIVARGA (see section 4.3).

In rats, STIVARGA/regorafenib metabolites are excreted in milk. STIVARGA could harm infant growth and development.

Fertility
Results from animal studies indicate that STIVARGA can impair male and female fertility.

4.7 Effects on ability to drive and use machines

STIVARGA may cause tremor and fatigue that may impair the patient's ability to drive or use machines.

4.8 Undesirable effects

a. Summary of the safety profile

The overall safety profile of STIVARGA is based on data from more than 4800 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 **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.

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

b. Tabulated summary of adverse reactions

Table 3: Adverse drug reactions reported in clinical trials <u>and postmarketing</u> in patients treated with STIVARGA.

System Organ Class (MedDRA)	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)	<u>Not known (not known (cannot be estimated from the available data)</u>
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	Thrombo-cytopenia Anaemia	Leucopenia			
Immune system disorders			Hypersensitivity reaction		

System Organ Class (MedDRA)	**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)**	**Not known (not known (cannot be estimated from the available data)**
Endocrine disorders		Hypothyroidism			
Metabolism and nutrition disorders	Decreased appetite and food intake	Hypokalemia Hypophosphatemia Hypocalcaemia Hyponatraemia Hypomagnesaemia Hyperuricaemia			
Nervous system disorders		Headache Tremor		Reversible posterior leukoencephalopathy syndrome (RPLS)	Hyperammonemic encephalopathy*
Cardiac disorders			Myocardial infarction Myocardial ischaemia		
Vascular disorders	Haemorrhage* Hypertension		Hypertensive crisis		
Respiratory, thoracic and mediastinal disorders	Dysphonia				
Gastrointestinal disorders	Diarrhoea Stomatitis Vomiting Nausea	Taste disorders Dry mouth Gastroesophageal reflux Gastroenteritis	Gastrointestinal perforation* Gastrointestinal fistula		
Hepatobiliary disorders	Hyperbilirubinaemia 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		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 International			

System Organ Class (MedDRA)	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)	Not known (not known (cannot be estimated from the available data)
		normalised ratio (INR)			

* 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

c. Description of selected adverse reactions

Haemorrhage:
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 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, the respiratory, gastrointestinal and genitourinary events.

Infection:
In the placebo-controlled phase III trials, infections were more often observed in patients treated with STIVARGA as 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 (2,65 %).
Fatal outcomes associated with infection were reported in 1, 0 % of patients treated with STIVARGA (1,0%) as compared to patients receiving placebo (0.3%) and were mainly respiratory events.

Hand-foot skin reaction:
In the placebo-controlled phase III trials, hand-foot skin reaction (HFSR) was reported in patients treated with STIVARGA. The reported incidences were, 51,4 % CRC, 66,7 % GIST and 51,6 % HCC).
Most cases of HFSR 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 HFSR was 17,1 % (CRC), 22,0 % (GIST) and 12, 3% (HCC).
A higher incidence of HFSR was observed in STIVARGA- treated Asian patients treated with STIVARGA (all grades: 74,8 % (CRC), 88,2 % (GIST) and 67,1 % HCC and Grade 3: 20,5 % (CRC), 23,5 % (GIST) and 13,5 % HCC).
4.8.1.1

Hypertension:
In the placebo-controlled phase III trials, the overall incidence of hypertension was higher in patients treated with STIVARGA as compared to patients receiving placebo (29,6% CRC, 60,6% GIST and 31,0% HCC in patients treated with STIVARGA).
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 % (GIST) and 15,2 % (HCC). One case of Grade 4 hypertension was reported in the GIST trial.

Severe liver injury:
In most cases of severe liver injury, liver dysfunction had an onset within the first 2 months of therapy and was characterised by a hepatocellular pattern of injury with transaminase elevations >20 x ULN,

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 %).

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

Table 4: Treatment-emergent laboratory test abnormalities reported in placebo-controlled phase III trials in patients with metastatic CRC.

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	83,6	1,8	0	61,0	0,8	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
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 3.
**International normalised ratio
*** Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0
- No Grade 4 denoted in Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0

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

* Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0
** International normalised ratio
- No Grade 4 denoted in CTCAE, Version 4.0

Table 6: Treatment-emergent laboratory test abnormalities reported in placebo-controlled phase III trial in patients with HCC (RESORCE)

Laboratory parameter, (in % of samples investigated)	**STIVARGA plus BSC[§] (N=374)**			**Placebo plus BSC[§] (N=193)**		
	All Grades*	**Grade 3***	**Grade 4***	**All Grades***	**Grade 3***	**Grade 4***
Blood and lymphatic system disorders						
Haemoglobin decreased	72,5	6,0	-	71,3	4,8	-
Platelet count decreased	63,1	4,6	0,8	50,0	0	0
Neutrophil count decreased	13,6	3,0	0	14,9	0,5	0,5
Lymphocyte count decreased	67,8	15,5	1,9	58,5	11,2	0,5
Metabolism and nutrition disorders						
Calcium decreased	23,4	0,3	0	10,1	0	0
Potassium decreased	30,7	3,8	0,5	9,0	2,1	0
Phosphate decreased	70,4	32,3	1,6	31,4	6,9	0
Hepatobiliary disorders						
Bilirubin increased	78,2	12,9	3,0	54,5	11,0	4,7
AST increased	92,7	16,2	1,6	84,3	17,3	2,6
ALT increased	70,4	5,7	0,5	58,6	4,7	0
Renal and urinary disorders						
Proteinuria	51,0	16,7	-	36,5	3,1	-
Investigations						
INR increased**	44,4	0,7	-	35,4	2,1	-
Lipase increased	40,5	11,2	3,0	27,0	7,6	1,1
Amylase increased	23,0	2,5	0,3	19,0	2,2	0,5

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
Alternatively, you can report to Bayer SafeTrack site (https://www.safetrack-public.bayer.com).

4.9 Overdose

The most frequently observed adverse reactions observed at high doses were dermatological events, dysphonia, diarrhoea, mucosal inflammation, dry mouth, decreased appetite, hypertension and fatigue. Overdosage is expected to exacerbate these adverse events.
There is no specific antidote for STIVARGA overdose. In the event of suspected overdose, STIVARGA should be immediately withheld, best supportive care instituted 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 metastasis (VEGFR3, PDGFR, FGFR) and tumour immunity (CSFIR).

Regorafenib inhibits mutated KIT, a major oncogenic driver in gastrointestinal stromal tumours, and thereby blocks tumour cell proliferation.

In preclinical studies regorafenib has demonstrated antitumour activity in a broad spectrum of tumour models including colorectal, gastrointestinal stromal and hepatocellular tumour models which is likely mediated by its antiangiogenic and antiproliferative 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 CORRECT study was in patients with metastatic colorectal cancer who have progressed after failure of other therapy.

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.

Patients continued therapy until disease progression or unacceptable toxicity.

The primary site of disease was colon 495 patients (65 %), rectum 220 patients (29 %), or both 44 patients (6 %). A KRAS mutation was reported in 430 (57 %) of patients at study entry.

Table 7: Efficacy Results from the CORRECT study.

Efficacy parameter	**Hazard Ratio* (95 % CI)**	**p-value**		**Median (95 % CI)**	
		(one-sided)	**(two-sided)**	**STIVARGA plus BSC (N=505)**	**Placebo plus BSC (N=255)**
Overall Survival	0,774 (0,636; 0,942)	0,005178	0,010356	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	<0,000001	1,9 months (1,9; 2,1)	1,7 months (1,7; 1,7)

* Hazard ratio < 1 favours STIVARGA

The CONCUR study 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. 120 patients in CONCUR were also previously treated with VEGF- or EGFR-targeted agents.

The addition of STIVARGA to BSC resulted in a median OS of 8,8 months [95% CI 7,3-9,8] vs. 6,3 months [4,8-7,6] in the placebo group). Progression-free survival was also significantly better with STIVARGA than it was with placebo (HR 0.31; 95% CI 0.22 – 0.44; one-sided p<0.0001), with a

median progression-free survival of 3.2 months (95% CI; 2.0 – 3.7) in the regorafenib group and 1.7 months (1.6 – 1.8) in the placebo group

Gastrointestinal stromal tumours (GIST):
The GRID study was in patients with gastrointestinal stromal tumours (GIST) previously treated with 2 tyrosine kinase inhibitors (imatinib and sunitinib).

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.
Patients continued therapy until disease progression or unacceptable toxicity.

Table 8: 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				

Hepatocellular carcinoma (HCC):
The RESORCE study was in patients with hepatocellular carcinoma who have been previously treated with sorafenib.

In total, 573 patients with HCC were randomized 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.

Table 9: 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)**
Overall Survival	0,624 (0,498, 0,785)	0,000017	10,6 months (9,1, 12,1)	7,8 months (6,3, 8,8)
Progression-Free Survival **	0,453 (0,369, 0,555)	<0,000001	3,1 months (2,8, 4,2)	1,5 months (1,4, 1,6)
Time To Progression **	0,439 (0.,355, 0,542)	<0,000001	3,2 months (2,9, 4,2)	1,5 months (1,4, 1,6)
§ Best Supportive Care * Hazard ratio < 1 favours STIVARGA ** based on investigator's assessment of tumour response by modified RECIST				

5.2 Pharmacokinetic properties

Absorption:
Regorafenib reaches mean peak plasma levels of about 2,5 mg/ℓ at about 3 to 4 hours after single oral dose of 160 mg regorafenib given as 4 tablets each containing 40 mg.
The concentrations of regorafenib and its major metabolites 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 and both active metabolites after a low-fat breakfast was 20 to 40 % higher compared to fasting.

Distribution:
Plasma concentration-time profiles for regorafenib as well as for the major active metabolites showed multiple peaks across the 24-hour dosing interval, which are attributed to enterohepatic circulation. Regorafenib is highly bound (99,5 %) to human plasma proteins.

Metabolism/biotransformation:
Regorafenib is metabolised 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. Protein binding of M-2 and M-5 is higher (99,8 % and 99,95 %, respectively) than that of regorafenib.

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

Elimination:
Following oral administration, mean elimination half-life for regorafenib and its metabolite M-2 in plasma ranged 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 a 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. Parent compound found in faeces could be derived from intestinal breakdown of conjugated metabolites, as well as unabsorbed medicine.

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.

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

Patients with hepatic impairment
The pharmacokinetics of STIVARGA in Child-Pugh A and B (mild to moderate) hepatic impairment patients were similar to the pharmacokinetics in patients with normal hepatic function.

STIVARGA is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) as it has not been studied in this population. STIVARGA is mainly eliminated via the liver, and exposure might be increased in this patient population.

Patients with renal impairment
Available clinical data and physiology-based pharmacokinetic modeling indicate similar steady-state 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. The pharmacokinetics of regorafenib has not been studied in patients with end-stage renal disease. However, physiology-based pharmacokinetic modeling does not predict any relevant change in exposure in these 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.

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 (36 months)

Once the bottle is opened STIVARGA 40 mg has shown to be stable for 7 weeks even without the desiccant. Thereafter, the product is to be discarded.

6.4 Special precautions for storage

Store at or below 30 ˚C.
Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

6.5 Nature and contents of container

White opaque 45 mℓ HDPE plastic bottle, closed with a PP/PP (polypropylene) white screw cap with sealing insert and child resistant and a molecular sieve desiccant.

Each bottle contains 28 film-coated tablets.

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Instructions for use/handling:

Press down the closure according to instructions on the cap while turning to the left. Keep the bottle tightly closed after first opening. The desiccant capsule must not be consumed but kept in the bottle.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd
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8 REGISTRATION NUMBER(S)

47/26/1005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 October 2014

10 DATE OF REVISION OF THE TEXT

26 June 2026