Bayer HealthCare

SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

STIVARGA® 40 mg

Film-coated tablet

COMPOSITION:

Each film-coated tablet contains 40,0 mg regorafenib.

Excipients:

Cellulose microcrystalline, croscarmellose sodium, iron oxide red E172, iron oxide yellow E172, lecithin (soya), macrogol, magnesium stearate, polyvinyl alcohol – partially hydrolysed, povidone, silica colloidal anhydrous, talc, titanium dioxide E171.

PHARMACOLOGICAL CLASSIFICATION:

A 26 Cytostatic agents

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Regorafenib is an oral tumour deactivation agent that potently blocks multiple protein kinases, including kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, $BRAF^{V600E}$), and the tumour microenvironment (PDGFR, FGFR). 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 and gastrointestinal stromal tumour models which is mediated by its antiangiogenic and antiproliferative effects. In addition, regorafenib has shown anti-metastatic effects *in vivo*. Major human metabolites (M-2 and M-5) exhibited similar efficacies compared to regorafenib in *in vitro* and *in vivo* models.

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.

Summary of clinical studies:

Metastatic colorectal cancer (CRC):

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

The primary efficacy endpoint was Overall Survival (OS). Secondary endpoints were Progression-Free Survival (PFS), objective tumour response rate and disease control rate.
In total, 760 patients were randomised 2:1 to receive 160 mg regorafenib (4 tablets STIVARGA each containing 40 mg regorafenib) orally once daily (N=505) plus Best Supportive Care (BSC) or matching placebo (N=255) plus BSC for 3 weeks on therapy followed by 1 week off therapy. The mean daily regorafenib dose received was 147 mg.

Patients continued therapy until disease progression or unacceptable toxicity. A pre-planned interim analysis for efficacy was performed when 432 deaths had occurred. The study was unblinded after this planned interim analysis of OS had crossed the pre-specified efficacy boundary, showing evidence of prolonged survival with STIVARGA plus BSC compared to placebo plus BSC.

Of the 760 randomised patients, the median age was 61 years, 461 (61 %) were male, 593 (78 %) were Caucasian, and all patients had baseline ECOG Performance Status of 0 or 1. 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.

Most patients (395) received 3 or fewer previous lines of treatment for metastatic disease. Therapies included treatment with fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if the patient was KRAS wild type, an anti-EGFR therapy.

The addition of STIVARGA to BSC resulted in significantly longer survival as compared to placebo plus BSC with a hazard ratio of 0,774 (p=0,005178 stratified log rank test) and a median OS of 6,4 months vs. 5,0 months [95 % CI 0,636; 0,942]. PFS was significantly longer in patients receiving STIVARGA plus BSC (HR: 0,494, p<0,000001).

Table 1: 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

Gastrointestinal stromal tumours (GIST):

The clinical efficacy and safety of STIVARGA have been evaluated in an international, multi-center, randomised, double-blind, placebo-controlled cross-over phase III study 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 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 as compared to placebo plus BSC with a hazard ratio of 0,268 [95 % CI 0,185; 0,388] and a median PFS of 4,8 months vs. 0,9 months (p<0,000001. The increase in PFS was independent of age, sex, geographic region, prior lines of treatment, ECOG performance status.

TTP was significantly longer in the patients receiving regorafenib plus BSC than in patients receiving placebo plus BSC with a hazard ratio of 0,248 [95 % CI 0,170; 0,364], and median TTP of 5,4 months versus 0,9 months (p<0,000001).
The HR of the OS analysis indicated a non-significant difference towards a positive treatment effect (HR=0,772 [95 % CI, 0,423; 1,408]; p=0,199; median OS was not reached in either arm) despite the post-progression cross-over of 85 % of patients initially randomised to the placebo arm.

Table 2: Efficacy Results from the GRID study.

Efficacy parameter	Hazard Ratio* (95 % CI)	p-value		Median (95 % CI)	
		(one-sided)	(two-sided)	Stivarga plus BSC (N=133)	Placebo plus BSC (N=66)
Progression-Free Survival	0,268 (0,185; 0,388)	<0,000001	<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	<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	0,398	NR**	NR**

* Hazard ratio < 1 favours STIVARGA
** NR: not reached

In addition, 56 placebo plus BSC patients received open-label regorafenib after cross-over following disease progression and a total of 41 regorafenib plus BSC patients continued regorafenib treatment after disease progression. The median secondary PFS (as measured by the investigator's assessment) were 5,0 and 4,5 months, respectively.

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 KRAS 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.

CONTRA-INDICATIONS:

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 "Pregnancy and Lactation")

WARNINGS AND SPECIAL PRECAUTIONS:

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 "Side Effects").

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 "Interactions"). 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 "Dosage and directions for use").

Close monitoring of overall safety is recommended in patients with mild or moderate hepatic impairment (see "Dosage and directions for use and Special precautions"). STIVARGA is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) as STIVARGA has not been studied in this population and exposure might be increased in these patients.

Haemorrhage:

STIVARGA has been associated with an increased incidence of haemorrhagic events, some of which were fatal (see "Side effects"). 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.

Cardiac ischaemia and infarction:

STIVARGA has been associated with an increased incidence of myocardial ischaemia and infarction (see "Side effects").

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 "Side effects").
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.

Gastrointestinal perforation and fistula:

Gastrointestinal perforation and fistulae have been reported in patients treated with STIVARGA (see "Side effects"). Discontinuation of STIVARGA is recommended in patients developing gastrointestinal perforation or fistula. The safety of re-initiating STIVARGA therapy following gastrointestinal perforation or fistula is not known.

Arterial hypertension:

STIVARGA has been associated with an increased incidence of arterial hypertension (see "Side effects"). 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 "DOSAGE AND DIRECTIONS FOR USE" 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 "Side effects"). 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 "Dosage and directions for use" subsection "Dose modification").

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). 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 "Dosage and directions for use" subsection "Dose modification").

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. No dose adjustment is required in these patients. Close monitoring of overall safety is also recommended.

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:

The steady-state exposure of STIVARGA is comparable in patients with mild renal impairment and patients with normal renal function. Limited data from phase I and II studies indicate that the range of exposure in patients with moderate renal impairment is comparable to that seen in patients with normal renal function. No dose adjustment is required in patients with mild or moderate renal impairment. The pharmacokinetics of STIVARGA has not been studied in patients with severe renal impairment or end-stage renal disease.

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.

INTERACTIONS:

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, phenobarbital 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 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 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 mean exposure (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:

In vitro data indicate that regorafenib is an inhibitor of Breast Cancer Resistance Protein (BCRP) and P-glycoprotein. Therefore administration of regorafenib may increase the plasma concentrations of concomitant medicines that are BCRP substrates, such as methotrexate, or P-glycoprotein substrates, such as digoxin.

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.

In a probe substrate study to evaluate the effect of 14 days of dosing with 160 mg regorafenib on the pharmacokinetics of CYP substrates, preliminary data show that co-administration of regorafenib and a single dose of 4 mg rosiglitazone (a substrate of CYP2C8) did not alter the exposure to rosiglitazone and its CYP2C8-selective metabolite. This indicates that regorafenib is not likely to be an *in vivo* inhibitor of CYP2C8 substrates.

Preliminary data also show that regorafenib had no effect on the pharmacokinetics of a single dose of 10 mg warfarin (a substrate of CYP2C9), suggesting the lack of any inhibition of CYP2C9 by regorafenib.

Preliminary data on co-administration of regorafenib and a single oral dose of 2 mg midazolam (a substrate of CYP3A4) show that there was evidence for a slight effect on midazolam exposure (24 % increase in AUC), suggestive of a weak CYP3A4 inhibition.

PREGNANCY AND LACTATION:

Pregnancy:

There are no data on the use of STIVARGA in pregnant women.
Based on its mechanism of action STIVARGA is suspected to cause foetal harm when administered during pregnancy. Animal studies have shown reproductive toxicity. STIVARGA should not be used during pregnancy. (See “Contra-indications”)

Lactation:

It is unknown whether STIVARGA/regorafenib metabolites are excreted in human milk.
In rats, STIVARGA/regorafenib metabolites are excreted in milk.

A risk to the breast-fed child cannot be excluded. STIVARGA could harm infant growth and development. Breast-feeding must be discontinued during treatment with STIVARGA. (See “Contra-indications”)

Fertility:

There are no data on the effect of STIVARGA on human fertility. Results from animal studies indicate that STIVARGA can impair male and female fertility.

Contraception:

Women of childbearing potential must be informed that STIVARGA 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.

DOSAGE AND DIRECTIONS FOR USE:

For oral use:

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.

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.

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

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 3 below.

Table 3: 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 to 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 to 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 to 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 to 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 to 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 4 below, (see "Warnings").

Table 4: 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 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.

SIDE EFFECTS:

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

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

Table 5: Adverse drug reactions reported in clinical trials in patients treated with STIVARGA.

System Organ Class (MedDRA)	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10 000 to < 1/1000)**
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		
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)
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	Hyperbilirubina-emia	Increase in transaminases	Severe liver injury*#	
Skin and subcutaneous tissue disorders	Hand-foot skin reaction** Rash Alopecia	Dry skin Exfoliative Rash	Nail disorder Erythema Multiforme	Stevens-Johnson syndrome Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders		Musculoskeletal stiffness		
Renal and urinary disorders		Proteinuria		
General disorders and administration site conditions	Asthenia/fatigue Pain Fever Mucosal inflammation			
Investigations	Weight loss	Increase in amylase Increase in lipase Abnormal International normalised ratio (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

Description of selected adverse reactions:

Haemorrhage:
In the two placebo-controlled phase III trials, the overall incidence of haemorrhage/bleeding events was 19,3 % in patients treated with STIVARGA. Most cases of bleeding events were mild to moderate in severity (Grades 1 and 2: 16,9 %), most notably epistaxis (7,6 %). Fatal events were uncommon (0,6 %), and involved the respiratory, gastrointestinal and genitourinary tracts.

Infection:
In the two placebo-controlled phase III trials, infections were more often observed in patients treated with STIVARGA as compared to patients receiving placebo (all grades: 31,0 % vs. 14,4 %). Most infections in patients treated with STIVARGA were mild to moderate in severity (Grades 1 and 2: 22,9 %), and included urinary tract infections (6,8 %) as well as mucocutaneous and systemic fungal infections (2,4 %). No difference in fatal outcomes associated with infection between treatment groups was observed (0,6 %, STIVARGA arm vs. 0,6 %, placebo arm).

Hand-foot skin reaction:
In the placebo-controlled metastatic CRC phase III trial, the overall incidence of hand-foot skin reaction was 45,2 % in patients treated with STIVARGA and 7,1 % in patients receiving placebo. In the placebo-controlled GIST phase III trial, the overall incidence of hand-foot skin reaction was 66,7 % in patients treated with STIVARGA and 15,2 % in patients receiving placebo. In both trials, most cases of hand-foot skin reaction in patients treated with STIVARGA appeared during the first cycle of treatment and were mild to moderate in severity (Grades 1 and 2: 28,6 %, CRC and 44,7 %, GIST). The incidence of Grade 3 hand-foot skin reaction was 16,6 % (CRC) and 22,0 % (GIST).

Hypertension:
In the placebo-controlled metastatic CRC phase III trial, the overall incidence of hypertension was 30,4 % in patients treated with STIVARGA and 7,9 % in patients receiving placebo. In the placebo-controlled GIST phase III trial, the overall incidence of hypertension was 59,1 % in patients treated with STIVARGA and 27,3 % in patients receiving placebo. In both trials, most cases of hypertension in patients treated with STIVARGA appeared during the first cycle of treatment and were mild to moderate in severity (Grades 1 and 2: 22, 8%, CRC and 31,1 %, GIST). The incidence of Grade 3 hypertension was 7,6 % (CRC) and 27,3 % (GIST). One case of Grade 4 hypertension was reported in the GIST trial.

Laboratory test abnormalities:
Treatment-emergent laboratory abnormalities observed in the placebo-controlled phase III trials are shown in Table 6 and Table 7 (see also "Warnings and Special Precautions").

Table 6: Treatment-emergent laboratory test abnormalities reported in placebo-controlled phase III trial in patients with metastatic CRC (CORRECT).

Laboratory Parameter, (in % of samples investigated)	STIVARGA plus BSC (N=500)			Placebo plus BSC (N=253)		
	All Grades*	Grade 3*	Grade 4*	All Grades*	Grade 3*	Grade 4*
Blood and lymphatic system disorders						
Haemoglobin decreased	78,5	4,7	0,6	66,3	2,8	0
Platelet count decreased	40,5	2,4	0,4	16,8	0,4	0
Neutrophil count decreased	2,8	0,6	0	0	0	0
Lymphocyte count decreased	54,1	9,3	0	34,4	3,2	0
Metabolism and nutrition disorders						
Calcium decreased	59,3	1,0	0,2	18,3	1,2	0
Potassium decreased	25,7	4,3	0	8,3	0,4	0
Phosphate decreased	57,4	30,5	0,6	11,1	3,6	0
Hepatobiliary disorders						
Bilirubin increased	44,6	9,6	2,6	17,1	5,2	3,2
AST increased	65,0	5,3	0,6	45,6	4,4	0,8
ALT increased	45,2	4,9	0,6	29,8	2,8	0,4
Renal and urinary disorders						
Proteinuria	59,7	0,4	0	34,1	0,4	0
Investigations						
INR increased**	23,7	4,2	-	16,6	1,6	-
Lipase increased	46,0	9,4	2,0	18,7	2,8	1,6
Amylase increased	25,5	2,2	0,4	16,7	2,0	0,4

* Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
** International normalised ratio
\- No Grade 4 denoted in Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0

Table 7: 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 Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The highest dose of STIVARGA studied clinically is 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 immediately be withheld, best supportive care instituted by a medical professional and the patient should be observed until clinical stabilisation.

IDENTIFICATION:

STIVARGA 40 mg film-coated tablets are light pink, oval, embossed with “BAYER” on one side and “40” on the other side.

PRESENTATION:

28 tablets with a molecular sieve desiccant in a 45 ml HDPE white opaque plastic bottle, closed with a PP/PP white screw cap with sealing insert and child resistant. Packs of 28’s or 84’s (3 bottles of 28’s) film-coated tablets.

STORAGE INSTRUCTIONS:

Store at or below 30 ˚C.
Store in the original package in order to protect from moisture.
Keep the desiccant in the bottle.
Keep the bottle tightly closed after first opening. Once the bottle is opened the medicinal product has shown to be stable for 28 days even without the desiccant. Thereafter, the product is to be discarded.

REGISTRATION NUMBER:

47/26/1005

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
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1609

DATE OF PUBLICATION OF THE PACKAGE INSERT:

02 October 2014