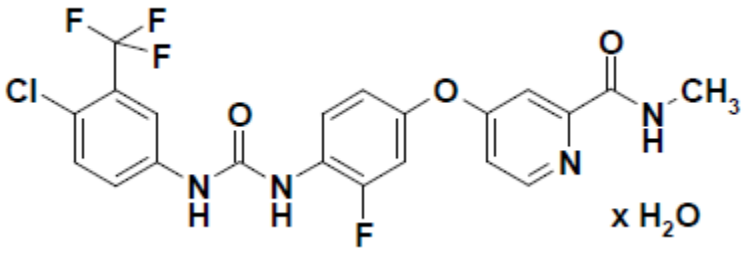
Attachment 1: Product information for AusPAR Stivarga Regorafenib Bayer Australia Ltd PM-2012-02342-3-4 Date of Finalisation 7 February 2014. This Product Information was approved at the time this AusPAR was published.

PRODUCT INFORMATION

STIVARGA® (regorafenib)

NAME OF THE MEDICINE

Regorafenib (as monohydrate) is 4-[4-({[4-chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-3-fluorophenoxy]-*N*methylpyridine-2-carboxamide monohydrate. Regorafenib (as monohydrate) has the following structural formula:



Molecular formula: $C_{21}H_{15}ClF_4N_4O_3.H_2O$

CAS number: 1019206-88-2

DESCRIPTION

Regorafenib monohydrate is a white to pink or brownish solid substance. Regorafenib monohydrate is practically insoluble in water between pH 1 and 13. Regorafenib monohydrate is not hygroscopic. Regorafenib monohydrate is practically insoluble in 0.1M HCl, slightly soluble in methanol; ethanol and sparingly soluble in acetone.

Each Stivarga tablet contains 40 mg regorafenib (as 41.49 mg regorafenib monohydrate) and the following excipients croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone, silica colloidal anhydrous, iron oxide red, iron oxide yellow, lecithin, macrogol 3350, polyvinyl alcohol, purified talc and titanium dioxide.

PHARMACOLOGY

Pharmacodynamic properties

Pharmacodynamic effects

Regorafenib is an oral anti-tumour agent that potently blocks multiple protein kinases, including kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF), and the tumour microenvironment (PDGFR, FGFR). In nonclinical studies regorafenib has demonstrated anti-tumour activity in a broad spectrum of *in vivo* tumour models presumed to be mediated both by its anti-angiogenic and anti-proliferative effects. In addition, regorafenib has shown anti-metastatic effects in breast cancer models *in vivo*. Major human metabolites M-2 (N-oxide) and M-5 (N-oxide and desmethyl) exhibited similar efficacies to regorafenib in *in vitro* and *in vivo* models.

Pharmacokinetics

Absorption

Regorafenib reaches mean peak plasma levels of approximately 2.5 mg/L at approximately three to four hours after a single oral dose of 160 mg regorafenib (given as four tablets each containing 40 mg). The mean relative bioavailability of the tablets compared to an oral solution is 69-83%.

The concentration of regorafenib and its major pharmacologically active metabolites M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl) 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 exposures of metabolite M-2 and M-5 were higher when regorafenib is given with low fat breakfast as compared to fasting condition and lower when given with a high fat meal as compared to fasting.

Distribution

Plasma concentration-time profiles for regorafenib as well as for the major circulating metabolites showed multiple peaks across the 24-hour dosing interval and can be attributed to enterohepatic circulation. *In vitro* protein binding of regorafenib to human plasma proteins is high (99.5%).

Metabolism

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. *In vitro* protein binding of M-2 and M-5 is higher (99.8% and 99.95%, respectively) than regorafenib.

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

Elimination

The mean elimination half-life for regorafenib and its metabolite M-2 in plasma ranges from 20 to 30 hours in different studies following oral administration. The mean elimination half-life for the metabolite M-5 is approximately 60 hours (ranges from 40 to 100 hours).

Approximately 90% of the radioactive dose was recovered within 12 days after administration, with approximately 71% of the dose excreted in faeces (47% as parent compound, 24% as metabolites), and approximately 19% of the dose excreted in urine as glucuronides. Urinary excretion of glucuronides decreased below 10% under steady-state conditions. Parent compound found in the faeces could be derived from unabsorbed drug, intestinal degradation of glucuronides or reduction of metabolite M-2.

Linearity/non-linearity

At steady state the systemic exposure of regorafenib increases proportionally up to doses of 60 mg and is less proportional at doses greater than 60 mg. Accumulation of regorafenib at steady state results in approximately 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 approximately 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. 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.

The pharmacokinetics of regorafenib has not been studied in patients with severe hepatic impairment (Child-Pugh C).

Renal impairment

The steady-state exposure of regorafenib, M-2 and M-5 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.

The pharmacokinetics of regorafenib 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 regorafenib at steady state in a dedicated QT study in male and female cancer patients.

CLINICAL TRIALS

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

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

In total, 760 patients were randomised 2:1 to receive 160 mg regorafenib (four Stivarga tablets each containing 40 mg regorafenib) orally once daily (N=505) plus Best Supportive Care (BSC) or matching placebo (N=255) plus BSC for three weeks on therapy followed by one 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 as OS had crossed the pre-specified efficacy boundary, showing evidence of prolonged survival with Stivarga plus BSC compared to placebo plus BSC. The median (range) duration of treatment (months) in patients treated with Stivarga was 1.7 (0.1 – 10.8) and with placebo was 1.6 (0.1 – 8.9).

Of the 760 randomised patients, the median age was 61 years, 61% were male, 78% were Caucasian, and all patients had baseline ECOG (Eastern Cooperative Oncology Group) Performance Status (PS) of 0 or 1. Please refer to Table 1 for the Demographic data from the trial. The primary site of disease was colon (65%), rectum (29%), or both (6%). A KRAS (Kirsten rat sarcoma viral oncogene homolog) mutation was reported in 57% of patients at study entry.

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

Table 1: Demographic data

Demographic details	Stivarga + BSC	Placebo + BSC
Age (mean, range)	60.7 years (22 – 82)	60.1 years (25 – 85)
Gender		
Male	61.6%	60.0%
Ethnicity		
Caucasian	77.6%	78.8%
Asian	15.0%	13.7%
Black	1.2%	3.1%
Other	<1%	<1%
Not reported	5.7%	3.9%
ECOG status		
0	52.5%	57.3%
Primary site of disease		
Colon	64.0%	67.5%
Rectum	29.9%	27.1%
Colon and rectum	5.9%	5.5%

The addition of Stivarga to BSC resulted in significantly longer survival 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] (refer to Table 2 and Figure 1). PFS was significantly longer in patients receiving Stivarga plus BSC (HR: 0.494, p<0.000001, see Table 2 and Figure 2).

Table 2: Efficacy results from the CORRECT study

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

* Hazard ratio < 1 favours Stivarga
** Stratified by geographic region and time from diagnosis of metastatic disease.
*** Based on Investigator's assessment of tumour response

Figure 1: Kaplan-Meier curve of Overall Survival

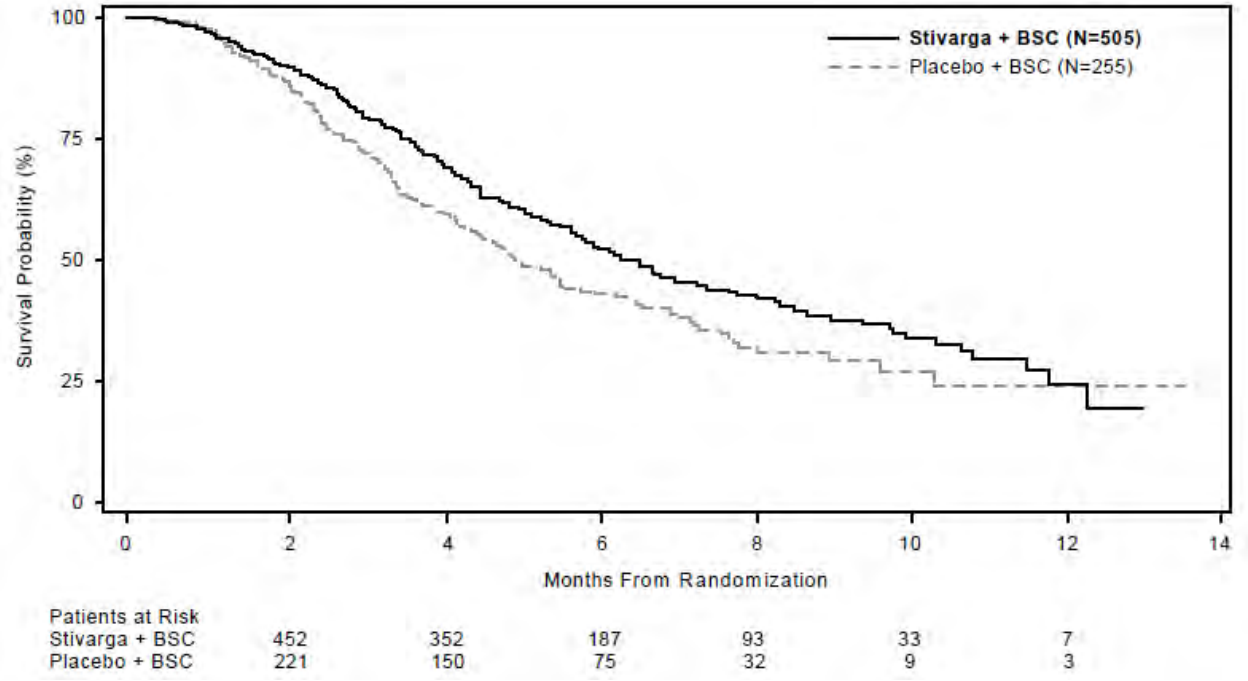
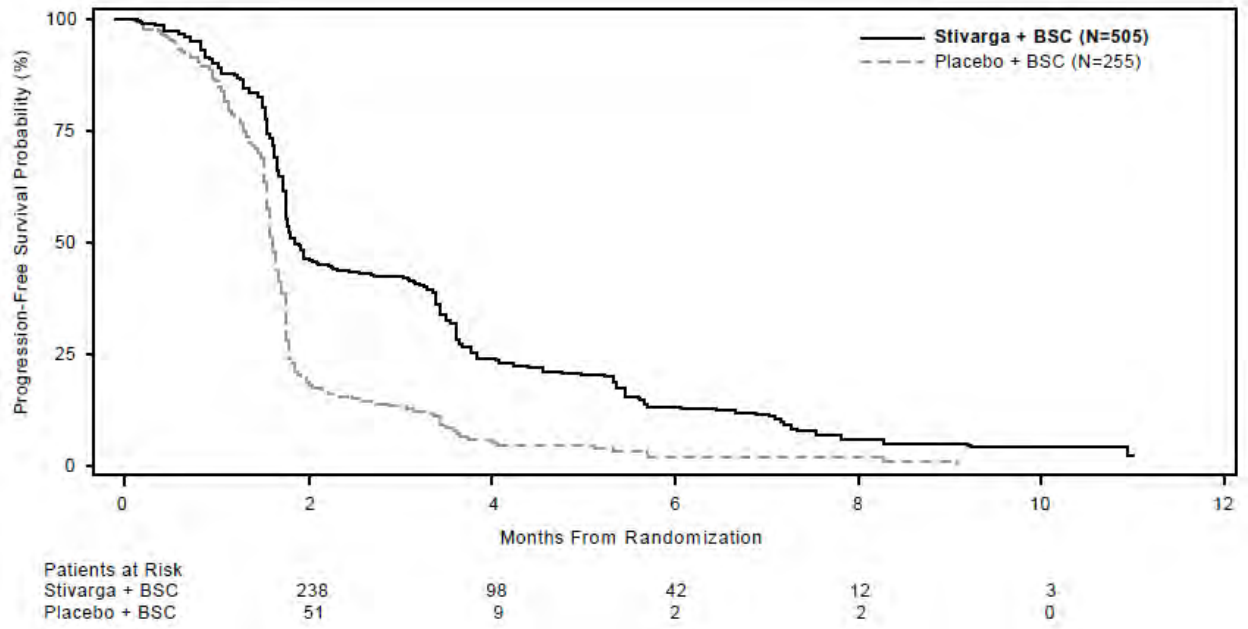


Figure 2: Kaplan-Meier curve of Progression-Free Survival



The response rate (complete response or partial response) was 1% and 0.4% (p=0.188432) for Stivarga and placebo treated patients respectively. The disease control rate (complete response or partial response or stable disease) was significantly higher in patients treated with Stivarga (41.0% vs 14.9%, p<0.000001).

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 showed a treatment effect favouring the regorafenib regimen over the placebo regimen.

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

INDICATIONS

Stivarga is indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients contained in Stivarga.

PRECAUTIONS

Hepatotoxicity

Severe drug induced liver injury with fatal outcome has been observed in patients receiving Stivarga. Liver biopsy results, when available, showed hepatocyte necrosis with lymphocyte infiltration. All patients with hepatic failure had metastatic disease in the liver (see Adverse Effects).

Abnormalities of liver function tests (alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) have been frequently observed in patients treated with Stivarga. 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 two months of treatment. Thereafter, periodic monitoring should be continued at least monthly and as clinically indicated. Monitor liver function tests weekly in patients experiencing elevated liver function tests until improvement to less than 3 times the ULN or baseline.

Regorafenib is a uridine diphosphate glucuronosyl transferase UGT1A1 inhibitor (see Interactions with other Medicines). Mild, 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 should be followed. This is outlined in Table 6: Recommended measures and dose modifications in case of drug-related liver function tests abnormalities found in Dosage and Administration – Dose modification section.

Since limited data is available for patients with pre-existing moderate hepatic impairment (Child-Pugh B) and regorafenib has not been studied in patients with severe hepatic impairment (Child-Pugh C), close monitoring of overall safety is recommended in these patients (see Dosage and Administration – Patients with hepatic impairment).

Haemorrhage

Stivarga has been associated with an increased incidence of haemorrhagic events, some of which were fatal (refer to Adverse Effects). Fatal haemorrhage was observed in patients treated with Stivarga and involved the respiratory, gastrointestinal, or genitourinary tracts.

Blood counts and coagulation parameters should be monitored in patients with conditions predispose to bleeding, and in those treated with anti-coagulants (e.g. warfarin) or other concomitant medications that increase the risk of bleeding. International normalised ratio (INR) values are to be more frequently monitored in patients receiving warfarin.

Permanently discontinue Stivarga in patients with severe or life-threatening haemorrhage.

Cardiac ischaemia and infarction

Stivarga has been associated with an increased incidence of myocardial ischaemia and infarction(see Adverse Effects).

Patients with a history of ischaemic heart disease should be monitored for clinical signs and symptoms of myocardial ischaemia. In patients who develop new or acute onset cardiac

ischaemia and/or infarction, interruption of Stivarga is recommended until resolution. The decision to re-initiate treatment with Stivarga 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 differences were observed between Stivarga and placebo in the incidence of clinically relevant cardiac arrhythmias or heart failure.

Reversible Posterior Leukoencephalopathy Syndrome

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported in association with Stivarga treatment (see Adverse 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 having previously experienced RPLS is not known.

Gastrointestinal perforation and fistula

Gastrointestinal perforation and fistula have been reported in patients treated with Stivarga (refer to Adverse Effects). These events are also known to be common disease-related complications in patients with intra-abdominal malignancies.

Permanently discontinue Stivarga in patients who develop gastrointestinal perforation or fistula.

Arterial hypertension

Stivarga has been associated with an increased incidence of arterial hypertension (see Adverse Effects). The onset of hypertension occurred during the first cycle of treatment in most patients who developed hypertension.

Hypertensive crisis was observed in patients treated with Stivarga.

Do not initiate Stivarga unless blood pressure is adequately controlled. Monitor blood pressure weekly for the first 6 weeks of treatment and then every cycle, or more frequently, as clinically indicated. Temporarily or permanently withhold Stivarga for severe or uncontrolled hypertension (see Dosage and Administration – 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, medicines with anti-angiogenic properties may suppress or interfere with wound healing; treatment with regorafenib should be stopped at least 2 weeks prior to scheduled surgery. The decision to resume after surgery should be based on clinical judgement of adequate wound healing.

Stivarga should be discontinued in patients with wound dehiscence.

Dermatological toxicity

Hand-foot skin reaction (HFSR)/palmar-plantar erythrodysaesthesia syndrome) and rash represent the most frequently observed dermatological adverse drug reactions with Stivarga (see Adverse 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.

Stevens-Johnson syndrome and toxic epidermal necrolysis were rarely observed in patients treated with Stivarga.

Dose reduction and/or temporary interruption of Stivarga, or in severe or persistent cases, permanent discontinuation of Stivarga should be considered (see Dosage and Administration–Dose modification).

Biochemical and metabolic laboratory test abnormalities

Stivarga has been associated with an increased incidence of electrolyte abnormalities (including hypophosphatemia, hypocalcaemia, hyponatremia and hypokalaemia) and metabolic abnormalities (including increases in thyroid stimulating hormone, lipase and amylase).

The abnormalities are generally 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 Administration - Dose modification).

Effects on Fertility

There is no data on the effect of Stivarga on human fertility. Based on histological changes (mostly atrophic) in the testes, ovaries and uterus observed after repeated dosing with regorafenib in rats and dogs at exposures below the anticipated human exposure (based on AUC), regorafenib has the potential to adversely affect male and female reproduction in humans.

Women of childbearing potential must be informed that regorafenib may cause fetal harm.

Use in Pregnancy

Pregnancy Category D.

There are no adequate or well-controlled studies with Stivarga in pregnant women. Based on its mechanism of action and findings in animal studies, regorafenib may cause fetal harm when administered during pregnancy.

A teratogenic effect was observed in pregnant rats and rabbits treated orally with regorafenib during the period of organogenesis at exposures below the anticipated human exposure (based on AUC). The main findings were malformations of the urinary system (rabbits only), the heart and major vessels, and the skeleton and embryofetal deaths. Regorafenib/metabolites crossed the placenta in rats.

Stivarga should not be used during pregnancy unless necessary and after careful consideration of the benefits for the mother and the risk to the fetus. Women of childbearing potential and men should ensure effective contraception during treatment and up to 8 weeks after completion of therapy.

Use in Lactation

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

A risk to the breast-fed child cannot be excluded. Regorafenib could harm infant growth and development. Breast-feeding must be discontinued during treatment with Stivarga.

Use in Children

The safety and efficacy of Stivarga in children and adolescents below 18 years of age have not been established.

Use in the Elderly

In clinical studies no relevant differences in exposure, safety or efficacy were observed between elderly (65 years and older) and younger patients. No dose adjustment is necessary in elderly patients.

Patients with hepatic impairment

In clinical studies, no relevant differences in 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 limited data is available in patients with moderate hepatic impairment (Child-Pugh B) and regorafenib has not been studied in patients with severe hepatic impairment (Child-Pugh C), no dose recommendation can be provided. Close monitoring of overall safety is recommended in these patients (see Precautions).

Patients with renal impairment

In clinical studies, no relevant differences in safety or efficacy were observed in patients with mild or moderate renal impairment and patients with normal renal function. No dose adjustment is required in patients with mild or moderate renal impairment (see Pharmacokinetics). No data is available for patients with severe renal impairment or end-stage renal disease.

Carcinogenicity

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

Genotoxicity

There was no indication of a genotoxic potential for regorafenib when tested in standard assays *in vitro* (bacterial gene mutation and chromosomal aberration assay in Chinese hamster V79 cells) and *in vivo* (mouse micronucleus test). The N-oxide and N-desmethyl metabolite (M-5), a major human active metabolite, did not induce gene mutation or chromosome aberration in the *in vitro* assays. The other major human active metabolite, M-2 (N-oxide), was negative in the bacterial gene mutation test, but was positive in the chromosomal aberration assay.

Systemic toxicity

After repeated dosing in mice, rats and dogs, adverse effects were observed in a number of organs, primarily in the kidneys, liver, digestive tract, heart, thyroid gland, lympho-/hematopoietic system, endocrine system, reproductive system and skin. 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 were observed in young and growing rats and indicate a potential risk for children and adolescents.

INTERACTIONS WITH OTHER MEDICINES

Inhibitors/inducers of CYP3A4

In vitro data indicate that regorafenib is metabolised largely 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 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 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 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 mean exposure (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, rifabutin, dexamethasone and St John's Wort) may also increase metabolism of regorafenib. Since a reduction in plasma regorafenib concentrations may result in 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 and its active metabolite M-2 inhibit glucuronidation mediated by uridine diphosphate glucuronosyl transferases UGT1A1 and UGT1A9, and the active metabolite M-5 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) of SN-38, a substrate of UGT1A1 and an active metabolite of irinotecan. An increase in mean exposure (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. The clinical significance of these findings is unknown.

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

In vitro data indicate that regorafenib is an inhibitor of BCRP and P-glycoprotein at clinically relevant concentrations. 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 (K_i value of 0.6 µM), CYP2C9 (K_i value of 4.7 µM) and CYP2B6 (K_i value of 5.2 µM) at concentrations which are achieved *in vivo* at steady state (peak plasma concentration of 8.1 µM). The *in vitro* inhibitory potency towards CYP3A4 (K_i value of 11.1 µM) and CYP2C19 (K_i value of 16.4 µM) was less pronounced. The active metabolite, M-2, showed a broadly similar CYP isoform inhibitory profile to parent drug while M-5 only inhibited CYP2C8 at clinically relevant concentrations.

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 CYP2C8 (rosiglitazone) CYP2C9 (S-warfarin), CYP2C19 (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 Precautions).

Antibiotics

The concentration-time profile indicates that regorafenib and its metabolites may undergo enterohepatic circulation (refer to Pharmacokinetics). Co-administration of antibiotics affecting the flora of the gastrointestinal tract may interfere with the enterohepatic circulation of regorafenib and may result in decreased regorafenib exposure. The clinical significance of these potential interactions is unknown, but may result in decreased efficacy of regorafenib.

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.

ADVERSE EFFECTS

Summary of the safety profile

The overall safety profile of Stivarga is based on data from more than 1,100 treated patients in clinical trials including placebo-controlled Phase III data for 500 patients with metastatic colorectal cancer.

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

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

The safety data in the pivotal study (CORRECT) were derived from a randomised (2:1), double-blind, placebo controlled trial in which 500 patients with previously treated metastatic colorectal cancer received Stivarga as a single agent at the dose of 160 mg daily for the first 3 weeks of each 4 week treatment cycle and 253 patients received placebo.

The incidence of severe treatment emergent adverse events (TEAEs) (≥ Grade 3) was higher with regorafenib (78%) than placebo (49%).

The rate of death due to adverse events not associated with disease progression was slightly higher with regorafenib (1.6% vs 1.2%). Five deaths were considered to be regorafenib-related: one case each of liver dysfunction; sudden death; cerebrovascular incident; pulmonary haemorrhage, bronchus; haemorrhage, gastrointestinal, anus and haemorrhage, genitourinary, vagina (the last two occurred in one patient).

Overall treatment discontinuation due to adverse drug reactions (all grades) was reported in 8.2% of patients treated with Stivarga compared to 1.2% of patients who received placebo. Hand foot skin reaction and rash were the most common reasons leading to treatment discontinuation of Stivarga.

A dose modification due to adverse events occurred in 67% and 22% of patients in the Stivarga and placebo group, respectively. The rates of dose reductions were also higher with Stivarga (38% vs 3%) as were the rates of dose interruptions (61% vs 22%) and treatment cessations (18% vs 13%) compared to placebo.

Table 3 compares the incidence of adverse reactions (≥10%) in patients receiving Stivarga and reported more commonly than in patients receiving placebo in the pivotal CORRECT study.

Table 3: Adverse drug reactions (≥10%) reported in patients treated with Stivarga and reported more commonly than in patients receiving placebo

Adverse Reactions	Stivarga (n=500)		Placebo (n=253)	
	Grade		Grade	
	All %	≥ 3 %	All %	≥ 3 %
General disorders and administration site conditions				
Asthenia/fatigue	64	15	46	11
Pain	29	3	21	2
Fever	28	2	15	0
Mucosal inflammation	16	2	2	0
Metabolism and nutrition disorders				
Decreased appetite and food intake	47	5	28	4
Skin and subcutaneous tissue disorders				
HFSR/PPE	45	17	7	0
Rash	26	6	4	<1
Gastrointestinal disorders				
Diarrhoea	43	8	17	2
Stomatitis	18	2	4	0
Investigations				
Weight loss	32	<1	10	0
Infections and infestations				
Infection	31	9	17	6
Vascular disorders				
Hypertension	30	8	8	<1
Haemorrhage*	21	1	8	1
Respiratory, thoracic and mediastinal disorders				
Dysphonia	30	0	6	0
Nervous system disorders				
Headache	10	<1	7	0
Blood and lymphatic system disorders				
Thrombocytopenia	15	3	2	<1
Anaemia	14	5	12	3
Hepatobiliary disorders				
Hyperbilirubinemia	19	7	9	6

* fatal outcomes observed

In the pivotal CORRECT study, other adverse reactions observed more commonly in patients treated with regorafenib than placebo and that occurred in <10% (all grades) were:

- dry skin (8.8% vs 3.2%)
- alopecia (7.6% vs 1.6%)
- taste disorder (7.6% vs 2.4%)
- hypophosphatemia (6.4% vs 0.8%)
- musculoskeletal stiffness (6.0% vs 2.0%)
- hyponatremia (5.8% vs 2.4%)
- leukopenia (4.2% vs 0.8%)
- increase in amylase (3.0% vs 0.4%)
- hypomagnesemia (2.2% vs 0.4%)
- gastroesophageal reflux (1.4% vs 0%)
- gastroenteritis (1.2% vs 0.4%)
- exfoliative rash (1.4% vs 0.4%)
- gastrointestinal fistula (0.8% vs 0.4%)
- myocardial infarction (0.4% vs 0%)
- proteinuria (8.6% vs 2.4%)
- hypokalemia (7.6% vs 1.9%)
- increase in transaminases (7.6% vs 4.4%)
- increase in lipase (6.2% vs 1.2%)
- hypocalcemia (5.8% vs 0.4%)
- dry mouth (4.8% vs 2.0%)
- hypothyroidism (4.2% vs 0.4%)
- abnormal international normalised ratio (INR) (2.4% vs 0.8%)
- tremor (2.0% vs 0%)
- hyperuricemia (1.2% vs 0%)
- nail disorder (1.0% vs 0%)
- erythema multiforme (0.8% vs 0.4%)
- myocardial ischemia (0.6% vs 0.4%)

Other adverse reactions were observed in patients treated with Stivarga in open-label or placebo-controlled clinical trials: gastrointestinal perforation* (0.6%), severe liver injury*¥ (0.3%), hypertensive crisis (0.2%), toxic epidermal necrolysis (TEN) (0.09%), reversible posterior leukoencephalopathy syndrome (RPLS) (0.08%), Stevens-Johnson syndrome (SJS) (0.05%) and keratoacanthoma/squamous cell carcinoma of the skin (0.05%).

*fatal outcome has been observed

¥According to drug-induced liver injury (DILI) criteria of the international DILI expert working group.

Laboratory abnormalities

Table 4 compares the incidence of laboratory test abnormalities in patients receiving Stivarga and in patients receiving placebo in the pivotal CORRECT study

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

Laboratory Parameter	Stivarga (N=500 [a])			Placebo (N=253 [a])		
	Grade [b]			Grade [b]		
	All %	3 %	4 %	All %	3 %	4 %
Blood and lymphatic						

Laboratory Parameter	Stivarga (N=500 [a])			Placebo (N=253 [a])		
	Grade [b]			Grade [b]		
	All %	3 %	4 %	All %	3 %	4 %
system disorders						
Anaemia	79	5	1	66	3	0
Thrombocytopenia	41	2	<1	17	<1	0
Neutropenia	3	1	0	0	0	0
Lymphopenia	54	9	0	34	3	0
Metabolism and nutrition disorders						
Hypocalcemia	59	1	<1	18	1	0
Hypokalemia	26	4	0	8	<1	0
Hyponatremia	30	7	1	22	4	0
Hypophosphatemia	57	31	1	11	4	0
Hepatobiliary disorders						
Hyperbilirubinemia	45	10	3	17	5	3
Increased AST	65	5	1	46	4	1
Increased ALT	45	5	1	30	3	<1
Renal and urinary disorders						
Proteinuria	60	<1	0	34	<1	0
Investigations						
Increased INR [c]	24	4	N/A	17	2	N/A
Increased Lipase	46	9	2	19	3	2
Increased Amylase	26	2	<1	17	2	<1

[a] % based on number of patients with post-baseline samples which may be less than 500 (regorafenib) or 253 (placebo).
[b] Common Terminology Criteria for Adverse Events (CTCAE), v3.0.
[c] International normalised ratio: No Grade 4 denoted in CTCAE, v3.0.

Description of selected adverse reactions

Haemorrhage
In the placebo-controlled Phase III trial in patients with metastatic CRC, the overall incidence of haemorrhage/bleeding events was 21.4% in patients treated with Stivarga. Most cases of bleeding events were mild to moderate in severity (Grades 1 and 2: 19.2%), most notably epistaxis (8.8%). Fatal events were uncommon (0.8%), and involved the respiratory, gastrointestinal and genitourinary tracts.

Infection
Infections were more often observed in patients treated with Stivarga compared to patients receiving placebo (all grades: 30.8% vs. 17.0%). Most infections in patients treated with Stivarga were mild to moderate in severity (Grades 1 and 2: 22.0%), and included urinary tract infections (7.2%) as well as mucocutaneous and systemic fungal infections (6.6%). No difference in fatal outcomes associated with infection between treatment groups was observed (0.6%, Stivarga arm vs. 0.8%, 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. Most cases of hand-foot skin reaction were mild to moderate in severity (Grades 1 and 2: 30.4%) and most appeared during the first cycle of treatment with Stivarga. The incidence of Grade 3 hand-foot skin reaction was 16.6%.

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. 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%). The incidence of Grade 3 hypertension was 7.6%.

DOSAGE AND ADMINISTRATION

Take four Stivarga (40 mg) tablets daily at the same time each day for three weeks on therapy (21 days) followed by one week off therapy (7 days) to comprise a cycle of four weeks (28 days) (see Pharmacokinetics – Absorption). The tablets should be swallowed whole with water after a low fat meal (ideally at breakfast) that contains less than 30% fat. Example of a low fat meal include one cup of cereal, 250 mL or one glass of skimmed milk, one slice of toast with jam, apple juice and one cup of coffee or tea (520 calories, 2 g fat, 17 g protein, 93 g of carbohydrate).

The recommended daily dose is 160 mg and contains 2.427 mmol (equivalent to 55.8 mg) of sodium per daily dose.

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 Precautions).

Dose modification/discontinuations

Dose interruptions and/or dose reductions or dose discontinuations 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.

Discontinue Stivarga permanently for (see Precautions):

- Severe and persistent hepatotoxicity
- Severe or life-threatening haemorrhage
- Severe and persistent HFSR
- Hypertensive crisis
- RPLS
- Gastrointestinal perforation or fistula
- Development of new or acute onset cardiac ischaemia and/or infarction if not resolved after interruption
- Wound dehiscence
- Significant biochemical and metabolic abnormalities
- Failure to tolerate 80 mg dose
- For any Grade 4 adverse reaction; only resume if the potential benefit outweighs the

Discontinue Stivarga permanently for (see Precautions):

risks

Interrupt Stivarga for the following:

- Symptomatic Grade 2 hypertension
- Any Grade 3 or 4 adverse reaction
- Surgical procedures
- Development of new or acute onset cardiac ischaemia and/or infarction

Reduce the dose of Stivarga to 120 mg:

- After recovery of any Grade 3 or 4 adverse reaction

Reduce the dose of Stivarga to 80 mg:

- After recovery of any Grade 3 or 4 adverse reaction at the 120 mg dose (except hepatotoxicity)

For recommended dose modifications and measures in case of hand-foot skin reaction (HFSR/palmar-plantar erythrodysesthesia syndrome) see Table 5.

Table 5: 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 doctor.
	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 doctor.
	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 doctor.
	4th occurrence	Discontinue treatment.

Skin toxicity grade	Occurrence	Recommended dose modification and measures
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 doctor.
	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 6 (refer to Precautions).

Table 6: 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.

OVERDOSAGE

There is no specific antidote for Stivarga overdose.

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.

In the event of suspected overdose, Stivarga should be withheld immediately with best supportive care initiated by a doctor. The patient should be observed until clinical stabilisation.

Contact Poisons Information Centre 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Stivarga tablets contain 40 mg regorafenib (as 41.49 mg regorafenib monohydrate). The tablets are light pink, oval embossed with 'BAYER' on one side and '40' on the other side. The tablets are packed in a white HDPE bottle containing a molecular sieve desiccant capsule.

Store Stivarga in the original package. Do not remove the desiccant. Keep the bottle tightly closed after first opening. Once the bottle is opened the tablets are to be discarded after 28 days.

Stivarga is available in pack sizes of 28, 28 (starter pack) and 84 (3 bottles of 28) tablets.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

BAYER AUSTRALIA LIMITED
ABN 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE ARTG

29 November 2013

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