

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use STIVARGA safely and effectively. See full prescribing information for STIVARGA.

**STIVARGA (regorafenib) tablets, oral
Initial U.S. Approval: 2012**

WARNING: HEPATOTOXICITY
See full prescribing information for complete boxed warning.
Severe and sometimes fatal hepatotoxicity has been observed in clinical trials. Monitor hepatic function prior to and during treatment. Interrupt and then reduce or discontinue Stivarga for hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis, depending upon severity and persistence. (2.2, 5.1)

----- **INDICATIONS AND USAGE** -----

Stivarga is a kinase inhibitor 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. (1)

----- **DOSAGE AND ADMINISTRATION** -----

- Recommended Dose: 160 mg orally, once daily for the first 21 days of each 28-day cycle. (2.1)
- Take Stivarga with food (a low-fat breakfast). (2.1, 12.3)

----- **DOSAGE FORMS AND STRENGTHS** -----

40 mg film-coated tablets (3)

----- **CONTRAINDICATIONS** -----

None.

----- **WARNINGS AND PRECAUTIONS** -----

- Hemorrhage: Permanently discontinue Stivarga for severe or life-threatening hemorrhage. (5.2)

- Dermatological toxicity: Interrupt and then reduce or discontinue Stivarga depending on severity and persistence of dermatologic toxicity. (5.3)
- Hypertension: Temporarily or permanently discontinue Stivarga for severe or uncontrolled hypertension. (5.4)
- Cardiac ischemia and infarction: Withhold Stivarga for new or acute cardiac ischemia/infarction and resume only after resolution of acute ischemic events. (5.5)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Discontinue Stivarga. (5.6)
- Gastrointestinal perforation or fistulae: Discontinue Stivarga. (5.7)
- Wound healing complications: Stop Stivarga before surgery. Discontinue in patients with wound dehiscence. (5.8)
- Embryofetal toxicity: Can cause fetal harm. Advise women of potential risk to a fetus. (5.9, 8.1)

----- **ADVERSE REACTIONS** -----

The most common adverse reactions (≥30%) are asthenia/fatigue, decreased appetite and food intake, hand-foot skin reaction (HFSR) [palmar-plantar erythrodysesthesia (PPE)], diarrhea, mucositis, weight loss, infection, hypertension, and dysphonia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----- **DRUG INTERACTIONS** -----

- Strong CYP3A4 inducers: Avoid strong CYP3A4 inducers. (7.1)
- Strong CYP3A4 inhibitors: Avoid strong CYP3A4 inhibitors. (7.2)

----- **USE IN SPECIFIC POPULATIONS** -----

Nursing Mothers: Discontinue drug or nursing, taking into consideration the importance of the drug to the mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2012

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FULL PRESCRIBING INFORMATION

WARNING: HEPATOTOXICITY

Severe and sometimes fatal hepatotoxicity has been observed in clinical trials. Monitor hepatic function prior to and during treatment. Interrupt and then reduce or discontinue Stivarga for hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis, depending upon severity and persistence [see *Dosage and Administration (2.2), Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose is 160 mg regorafenib (four 40 mg tablets) taken orally once daily for the first 21 days of each 28-day cycle. Continue treatment until disease progression or unacceptable toxicity.

Take Stivarga at the same time each day. Swallow tablet whole with a low-fat breakfast that contains less than 30% fat [see *Clinical Pharmacology (12.3)*]. Examples of a low-fat breakfast include 2 slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly, and 8 ounces of skim milk (319 calories and 8.2 g fat); or 1 cup of cereal, 8 ounces of skim milk, 1 slice of toast with jam, apple juice, and 1 cup of coffee or tea (520 calories and 2 g fat). Do not take two doses of Stivarga on the same day to make up for a missed dose from the previous day.

2.2 Dose Modifications

Interrupt Stivarga for the following:

- NCI CTCAE Version 3.0 (v3.0) Grade 2 hand-foot skin reaction (HFSR) [palmar-plantar erythrodysesthesia (PPE)] that is recurrent or does not improve within 7 days despite dose reduction; interrupt therapy for a minimum of 7 days for Grade 3 HFSR
- Symptomatic Grade 2 hypertension
- Any NCI CTCAE v3.0 Grade 3 or 4 adverse reaction

Reduce the dose of Stivarga to 120 mg:

- For the first occurrence of Grade 2 HFSR of any duration
- After recovery of any Grade 3 or 4 adverse reaction
- For Grade 3 aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) elevation; only resume if the potential benefit outweighs the risk of hepatotoxicity

Reduce the dose of Stivarga to 80 mg:

- For re-occurrence of Grade 2 HFSR at the 120 mg dose
- After recovery of any Grade 3 or 4 adverse reaction at the 120 mg dose (except hepatotoxicity)

Discontinue Stivarga permanently for the following:

- Failure to tolerate 80 mg dose
- Any occurrence of AST or ALT more than 20 times the upper limit of normal (ULN)
- Any occurrence of AST or ALT more than 3 times ULN with concurrent bilirubin more than 2 times ULN

- Re-occurrence of AST or ALT more than 5 times ULN despite dose reduction to 120 mg
- For any Grade 4 adverse reaction; only resume if the potential benefit outweighs the risks

3 DOSAGE FORMS AND STRENGTHS

Stivarga is a 40 mg, light pink, oval shaped, film-coated tablet, debossed with 'BAYER' on one side and '40' on the other side.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Severe drug induced liver injury with fatal outcome occurred in 0.3% of 1100 Stivarga-treated patients across all clinical trials. Liver biopsy results, when available, showed hepatocyte necrosis with lymphocyte infiltration. In Study 1, fatal hepatic failure occurred in 1.6% of patients in the regorafenib arm and 0.4% of patients in the placebo arm; all the patients with hepatic failure had metastatic disease in the liver.

Obtain liver function tests (ALT, AST and bilirubin) before initiation of Stivarga and monitor at least every two weeks during the first 2 months of treatment. Thereafter, monitor monthly or more frequently 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.

Temporarily hold and then reduce or permanently discontinue Stivarga depending on the severity and persistence of hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis [*see Dosage and Administration (2.2)*].

5.2 Hemorrhage

Stivarga caused an increased incidence of hemorrhage. The overall incidence (Grades 1-5) was 21% in Stivarga-treated patients compared to 8% in placebo-treated patients in Study 1. Fatal hemorrhage occurred in 4 of 500 (0.8%) of Stivarga-treated patients and involved the respiratory, gastrointestinal, or genitourinary tracts.

Permanently discontinue Stivarga in patients with severe or life-threatening hemorrhage. Monitor INR levels more frequently in patients receiving warfarin [*see Clinical Pharmacology (12.3)*].

5.3 Dermatological Toxicity

Stivarga caused an increased incidence of hand-foot skin reaction (HFSR) also known as palmar-plantar erythrodysesthesia (PPE) and rash frequently requiring dose modification. The overall incidence of HFSR (45% versus 7%) and the incidence of Grade 3 HFSR (17% versus 0) were increased in Stivarga-treated patients in Study 1. The overall incidence of rash (26% versus 4%) and the incidence of Grade 3 rash (6% versus <1%) were higher in Stivarga-treated patients in Study 1 [*see Adverse Reactions (6.1)*]. The onset of dermatologic toxicity occurred in the first cycle of treatment in most patients.

Temporarily hold and then reduce or permanently discontinue Stivarga depending on the severity and persistence of dermatologic toxicity [*see Dosage and Administration (2.2)*]. Institute supportive measures for symptomatic relief.

5.4 Hypertension

Stivarga caused an increased incidence of hypertension (30% of Stivarga-treated patients vs. 8% of placebo-treated patients in Study 1) [*see Adverse Reactions (6.1)*]. Hypertensive crisis occurred in 0.18% of 1100 Stivarga-treated patients

across all clinical trials. The onset of hypertension occurred during the first cycle of treatment in most patients. Do not initiate Stivarga until 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* (2.2)].

5.5 Cardiac Ischemia and Infarction

Stivarga increased the incidence of myocardial ischemia and infarction (1.2% for Stivarga-treated patients vs. 0.4% of placebo-treated patients) [see *Adverse Reactions* (6.1)].

Withhold Stivarga in patients who develop new or acute onset cardiac ischemia or infarction. Resume Stivarga only after resolution of acute cardiac ischemic events if the potential benefits outweigh the risks of further cardiac ischemia.

5.6 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

RPLS (also known as posterior reversible encephalopathy syndrome) occurred in one of 1100 Stivarga-treated patients across all clinical trials. Confirm the diagnosis of RPLS with MRI and discontinue Stivarga in patients who develop RPLS.

5.7 Gastrointestinal Perforation or Fistula

Gastrointestinal perforation or fistula occurred in 0.6% of 1100 patients treated with Stivarga across clinical trials. Permanently discontinue Stivarga in patients who develop gastrointestinal perforation or fistula.

5.8 Wound Healing Complications

No formal studies of the effect of regorafenib on wound healing have been conducted. Since vascular endothelial growth factor receptor (VEGFR) inhibitors such as regorafenib can impair wound healing, treatment with regorafenib should be stopped at least 2 weeks prior to scheduled surgery. The decision to resume regorafenib after surgery should be based on clinical judgment of adequate wound healing. Regorafenib should be discontinued in patients with wound dehiscence.

5.9 Embryo-Fetal Toxicity

Stivarga can cause fetal harm when administered to a pregnant woman. Regorafenib was embryolethal and teratogenic in rats and rabbits at exposures lower than human exposures at the recommended dose, with increased incidences of cardiovascular, genitourinary, and skeletal malformations. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see *Use in Specific Populations* (8.1)].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hepatotoxicity [See *Warnings and Precautions* (5.1)]
- Hemorrhage [See *Warnings and Precautions* (5.2)]
- Dermatological Toxicity [See *Warnings and Precautions* (5.3)]
- Hypertension [See *Warnings and Precautions* (5.4)]
- Cardiac Ischemia and Infarction [See *Warnings and Precautions* (5.5)]
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) [See *Warnings and Precautions* (5.6)]
- Gastrointestinal Perforation or Fistula [See *Warnings and Precautions* (5.7)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rate observed in practice.

The safety data described below, except where noted, are derived from a randomized (2:1), double-blind, placebo-controlled trial (Study 1) in which 500 patients (median age 61 years; 61% men) 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 (median age 61 years; 60% men) received placebo. The mean duration of therapy was 12 weeks for patients receiving Stivarga and 8 weeks for patients receiving placebo. Due to adverse reactions, 61% of the patients receiving Stivarga required a dose interruption and 38% of the patients had their dose reduced. Drug-related adverse reactions that resulted in treatment discontinuation were reported in 8.2% of Stivarga-treated patients compared to 1.2% of patients who received placebo. Skin toxicity (HFSR/PPE or rash) was the most common cause of permanent drug discontinuation.

The most frequently observed adverse drug reactions ($\geq 30\%$) in patients receiving Stivarga are asthenia/fatigue, decreased appetite and food intake, HFSR/PPE, diarrhea, mucositis, weight loss, infection, hypertension and dysphonia.

The most serious adverse drug reactions in patients receiving Stivarga are hepatotoxicity, hemorrhage, and gastrointestinal perforation.

Table 1 compares the incidence of adverse reactions ($\geq 10\%$) in patients receiving Stivarga and reported more commonly than in patients receiving placebo (Study 1).

Table 1: Adverse drug reactions ($\geq 10\%$) 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	9
Pain	29	3	21	2
Fever	28	2	15	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				
Diarrhea	43	8	17	2
Mucositis	33	4	5	0
Investigations				
Weight loss	32	<1	10	0
Infections and infestations				
Infection	31	9	17	6
Vascular disorders				
Hypertension	30	8	8	<1
Hemorrhage*	21	2	8	<1
Respiratory, thoracic and mediastinal disorders				
Dysphonia	30	0	6	0
Nervous system disorders				
Headache	10	<1	7	0

* fatal outcomes observed

Other clinically important adverse reactions observed more commonly in less than 10% of Stivarga-treated patients and at a higher incidence than in placebo-treated patients included the following: alopecia (7.6% vs. 1.6%), taste disorder (7.6% vs. 2.4%), musculoskeletal stiffness (6.0% vs. 2.0%), dry mouth (4.8% vs. 2.0%), hypothyroidism (4.2% vs. 0.4%), tremor (2.0% vs. 0.0), gastroesophageal reflux (1.4% vs. 0.0), and gastrointestinal fistula (0.8% vs. 0.4%).

Keratoacanthoma/squamous cell carcinoma of the skin occurred in 0.09% of 1100 Stivarga-treated patients across open-label or placebo-controlled clinical trials.

Laboratory Abnormalities

Laboratory abnormalities observed in Study 1 are shown in Table 2.

Table 2: Laboratory test abnormalities reported in Study 1

Laboratory Parameter	Stivarga plus BSC (n=500*)			Placebo plus BSC (n=253*)		
	Grade**			Grade**		
	All %	3 %	4 %	All %	3 %	4 %
Blood and lymphatic system disorders						
Anemia	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 ***	24	4	N/A	17	2	N/A
Increased Lipase	46	9	2	19	3	2
Increased Amylase	26	2	<1	17	2	<1

* % based on number of patients with post-baseline samples which may be less than 500 (regorafenib) or 253 (placebo)

** Common Terminology Criteria for Adverse Events (CTCAE), v3.0

*** International normalized ratio: No Grade 4 denoted in CTCAE, v3.0

7 DRUG INTERACTIONS

7.1 Effect of Strong CYP3A4 Inducers on Regorafenib

Co-administration of a strong CYP3A4 inducer (rifampin) with a single 160 mg dose of Stivarga decreased the mean exposure of regorafenib, increased the mean exposure of the active metabolite M-5, and resulted in no change in the mean exposure of the active metabolite M-2. Avoid concomitant use of strong CYP3A4 inducers (e.g. rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort) [see *Clinical Pharmacology* (12.3)].

7.2 Effect of Strong CYP3A4 Inhibitors on Regorafenib

Co-administration of a strong CYP3A4 inhibitor (ketoconazole) with a single 160 mg dose of Stivarga increased the mean exposure of regorafenib and decreased the mean exposure of the active metabolites M-2 and M-5. Avoid concomitant use of strong inhibitors of CYP3A4 activity (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) [see *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see Warnings and Precautions (5.9)]

Risk Summary

Based on its mechanism of action, Stivarga can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies with Stivarga in pregnant women. Regorafenib was embryolethal and teratogenic in rats and rabbits at exposures lower than human exposures at the recommended dose, with increased incidences of cardiovascular, genitourinary, and skeletal malformations. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Animal Data

In embryo-fetal development studies, a total loss of pregnancy (100% resorption of litter) was observed in rats at doses as low as 1 mg/kg (approximately 6% of the recommended human dose, based on body surface area) and in rabbits at doses as low as 1.6 mg/kg (approximately 25% of the human exposure at the clinically recommended dose measured by AUC).

In a single dose distribution study in pregnant rats, there was increased penetration of regorafenib across the blood-brain barrier in fetuses compared to dams. In a repeat dose study with daily administration of regorafenib to pregnant rats during organogenesis, findings included delayed ossification in fetuses at doses ≥ 0.8 mg/kg (approximately 5% of the recommended human dose based on body surface area) with dose-dependent increases in skeletal malformations including cleft palate and enlarged fontanelle at doses ≥ 1 mg/kg (approximately 10% of the clinical exposure based on AUC). At doses ≥ 1.6 mg/kg (approximately 11% of the recommended human dose based on body surface area), there were dose-dependent increases in the incidence of cardiovascular malformations, external abnormalities, diaphragmatic hernia, and dilation of the renal pelvis.

In pregnant rabbits administered regorafenib daily during organogenesis, there were findings of ventricular septal defects evident at the lowest tested dose of 0.4 mg/kg (approximately 7% of the AUC in patients at the recommended dose). At doses of ≥ 0.8 mg/kg (approximately 15% of the human exposure at the recommended human dose based on AUC), administration of regorafenib resulted in dose-dependent increases in the incidence of additional cardiovascular malformations and skeletal anomalies as well as significant adverse effects on the urinary system including missing kidney/ureter; small, deformed and malpositioned kidney; and hydronephrosis. The proportion of viable fetuses that were male decreased with increasing dose in two rabbit embryo-fetal toxicity studies.

8.3 Nursing Mothers

It is unknown whether regorafenib or its metabolites are excreted in human milk. In rats, regorafenib and its metabolites are excreted in milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Stivarga, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of Stivarga in pediatric patients less than 18 years of age have not been established.

In 28-day repeat dose studies in rats there were dose-dependent findings of dentin alteration and angiectasis. These findings were observed at regorafenib doses as low as 4 mg/kg (approximately 25% of the AUC in humans at the recommended dose). In 13-week repeat dose studies in dogs there were similar findings of dentin alteration at doses as low as 20 mg/kg (approximately 43% of the AUC in humans at the recommended dose). Administration of regorafenib in these animals also led to persistent growth and thickening of the femoral epiphyseal growth plate.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Stivarga, 39% were 65 and over, while 8% were 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Hepatic Impairment

No clinically important differences in the mean exposure of regorafenib or the active metabolites M-2 and M-5 were observed in patients with hepatocellular carcinoma and mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment compared to patients with normal hepatic function [see *Clinical Pharmacology (12.3)*]. No dose adjustment is recommended in patients with mild or moderate hepatic impairment. Closely monitor patients with hepatic impairment for adverse reactions [see *Warnings and Precautions (5.1)*].

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

8.7 Renal Impairment

No clinically relevant differences in the mean exposure of regorafenib and the active metabolites M-2 and M-5 were observed in patients with mild renal impairment (CLcr 60-89 mL/min/1.73m²) compared to patients with normal renal function following regorafenib 160 mg daily for 21 days [see *Clinical Pharmacology (12.3)*]. No dose adjustment is recommended for patients with mild renal impairment. Limited pharmacokinetic data are available from patients with moderate renal impairment (CLcr 30-59 mL/min/1.73m²). Stivarga has not been studied in patients with severe renal impairment or end-stage renal disease.

8.8 Females and Males of Reproductive Potential

Contraception

Use effective contraception during treatment and up to 2 months after completion of therapy.

Infertility

There are no data on the effect of Stivarga on human fertility. Results from animal studies indicate that regorafenib can impair male and female fertility [see *Nonclinical Toxicology (13.1)*].

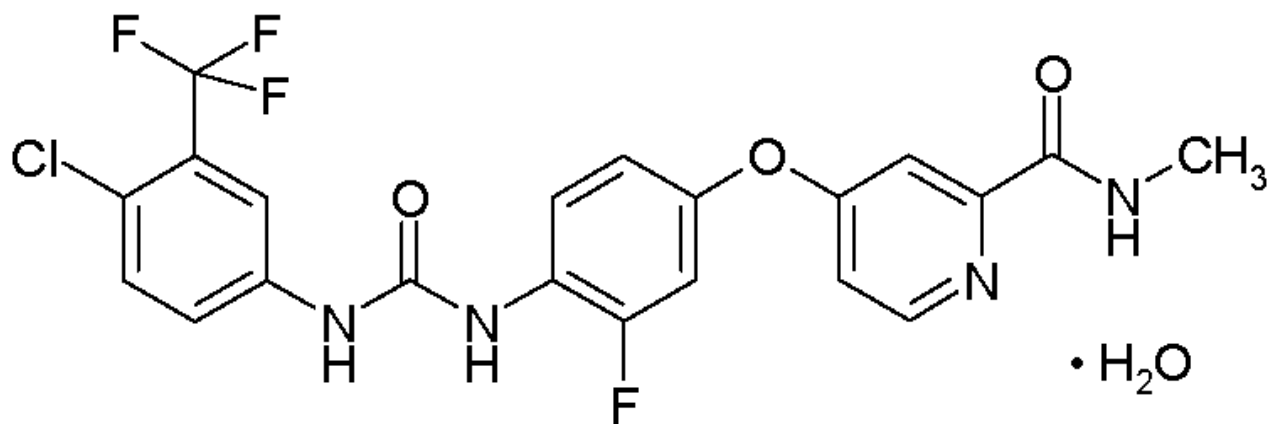
10 OVERDOSAGE

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, diarrhea, mucosal inflammation, dry mouth, decreased appetite, hypertension, and fatigue.

There is no specific antidote for Stivarga overdose. In the event of suspected overdose, interrupt Stivarga, institute supportive care, and observe until clinical stabilization.

11 DESCRIPTION

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



Regorafenib is a monohydrate and it has a molecular formula $C_{21}H_{15}ClF_4N_4O_3 \cdot H_2O$ and a molecular weight of 500.83. Regorafenib is practically insoluble in water, slightly soluble in acetonitrile, methanol, ethanol, and ethyl acetate and sparingly soluble in acetone.

Stivarga tablets for oral administration are formulated as light pink oval shaped tablets debossed with "BAYER" on one side and "40" on the other. Each tablet contains 40 mg of regorafenib in the anhydrous state, which corresponds to 41.49 mg of regorafenib monohydrate, and the following inactive ingredients: cellulose microcrystalline, croscarmellose sodium, magnesium stearate, povidone, and colloidal silicon dioxide. The film-coating contains the following inactive ingredients: ferric oxide red, ferric oxide yellow, lecithin (soy), polyethylene glycol 3350, polyvinyl alcohol, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. In *in vitro* biochemical or cellular assays, regorafenib or its major human active metabolites M-2 and M-5 inhibited the activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR- α , PDGFR- β , FGFR1, FGFR2, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, BRAF^{V600E}, SAPK2, PTK5, and Abl at concentrations of regorafenib that have been achieved clinically. In *in vivo* models, regorafenib demonstrated anti-angiogenic activity in a rat tumor model, and inhibition of tumor growth as well as anti-metastatic activity in several mouse xenograft models including some for human colorectal carcinoma.

12.3 Pharmacokinetics

Absorption

Following a single 160 mg dose of Stivarga in patients with advanced solid tumors, regorafenib reaches a geometric mean peak plasma level (C_{max}) of 2.5 $\mu\text{g/mL}$ at a median time of 4 hours and a geometric mean area under the plasma concentration vs. time curve (AUC) of 70.4 $\mu\text{g}\cdot\text{h/mL}$. The AUC of regorafenib at steady-state increases less than dose proportionally at doses greater than 60 mg. At steady-state, regorafenib reaches a geometric mean C_{max} of 3.9 $\mu\text{g/mL}$ and a geometric mean AUC of 58.3 $\mu\text{g}\cdot\text{h/mL}$. The coefficient of variation of AUC and C_{max} is between 35% and 44%.

The mean relative bioavailability of tablets compared to an oral solution is 69% to 83%.

In a food-effect study, 24 healthy men received a single 160 mg dose of Stivarga on three separate occasions: under a fasted state, with a high-fat meal and with a low-fat meal. A high-fat meal (945 calories and 54.6 g fat) increased the mean

AUC of regorafenib by 48% and decreased the mean AUC of the M-2 and M-5 metabolites by 20% and 51%, respectively, as compared to the fasted state. A low-fat meal (319 calories and 8.2 g fat) increased the mean AUC of regorafenib, M-2 and M-5 by 36%, 40% and 23%, respectively as compared to fasted conditions. Stivarga was administered with a low-fat meal in Study 1 [see *Dosage and Administration (2.1), Clinical Studies (14)*].

Distribution

Regorafenib undergoes enterohepatic circulation with multiple plasma concentration peaks observed across the 24-hour dosing interval. Regorafenib is highly bound (99.5%) to human plasma proteins.

Metabolism

Regorafenib is metabolized by CYP3A4 and UGT1A9. The main circulating metabolites of regorafenib measured at steady-state in human plasma are M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl), both of them having similar *in vitro* pharmacological activity and steady-state concentrations as regorafenib. M-2 and M-5 are highly protein bound (99.8% and 99.95%, respectively).

Elimination

Following a single 160 mg oral dose of Stivarga, the geometric mean (range) elimination half-lives for regorafenib and the M-2 metabolite in plasma are 28 hours (14 to 58 hours) and 25 hours (14 to 32 hours), respectively. M-5 has a longer mean (range) elimination half-life of 51 hours (32 to 70 hours).

Approximately 71% of a radiolabeled dose was excreted in feces (47% as parent compound, 24% as metabolites) and 19% of the dose was excreted in urine (17% as glucuronides) within 12 days after administration of a radiolabeled oral solution at a dose of 120 mg.

Patients with hepatic impairment

The pharmacokinetics of regorafenib, M-2, and M-5 were evaluated in 14 patients with hepatocellular carcinoma (HCC) and mild hepatic impairment (Child-Pugh A); 4 patients with HCC and moderate hepatic impairment (Child-Pugh B); and 10 patients with solid tumors and normal hepatic function after the administration of a single 100 mg dose of Stivarga. No clinically important differences in the mean exposure of regorafenib, M-2, or M-5 were observed in patients with mild or moderate hepatic impairment compared to the patients with normal hepatic function. The pharmacokinetics of regorafenib has not been studied in patients with severe hepatic impairment (Child-Pugh C).

Patients with renal impairment

The pharmacokinetics of regorafenib, M-2, and M-5 were evaluated in 10 patients with mild renal impairment (CL_{cr} 60-89 mL/min/1.73m²) and 18 patients with normal renal function following the administration of Stivarga at a dose of 160 mg daily for 21 days. No differences in the mean steady-state exposure of regorafenib, M-2, or M-5 were observed in patients with mild renal impairment compared to patients with normal renal function. Limited pharmacokinetic data are available from patients with moderate renal impairment (CL_{cr} 30-59 mL/min/1.73m²). The pharmacokinetics of regorafenib has not been studied in patients with severe renal impairment or end-stage renal disease.

Drug-drug interactions

In vitro screening on cytochrome P450 enzymes: *In vitro* studies with human hepatic microsomes or recombinant enzymes showed that regorafenib competitively inhibits CYP2C8, CYP2C9, CYP2B6, CYP3A4, and CYP2C19 with R₁ values > 1.1; M-2 inhibits CYP2C9, CYP2C8, CYP3A4, and CYP2D6 with R₁ values > 1.1 and M-5 inhibits CYP2C8 with a R₁ value > 1.1. *In vitro* studies with primary human hepatocytes showed that regorafenib is not expected to induce CYP1A2, CYP2B6, CYP2C19, and CYP3A4 enzyme activity.

In vitro screening on uridine diphosphate glucuronosyltransferases: *In vitro* studies with human hepatic microsomes showed that regorafenib, M-2, and M-5 competitively inhibits UGT1A9 and UGT1A1 at therapeutically relevant concentrations.

In vitro screening on transporters: *In vitro* data showed that regorafenib is an inhibitor of ABCG2 (Breast Cancer Resistance Protein) and ABCB1 (P-glycoprotein).

Effect of CYP3A4 Strong Inducers on Regorafenib: Twenty-two healthy men received a single 160 mg dose of Stivarga alone and then 7 days after starting rifampin. Rifampin, a strong CYP3A4 inducer, was administered at a dose of 600 mg daily for 9 days. The mean AUC of regorafenib decreased by 50% and mean AUC of M-5 increased by 264%. No change in the mean AUC of M-2 was observed [see *Drug Interactions (7.1)*].

Effect of CYP3A4 Strong Inhibitors on Regorafenib: Eighteen healthy men received a single 160 mg dose of Stivarga alone and then 5 days after starting ketoconazole. Ketoconazole, a strong CYP3A4 inhibitor, was administered at a dose of 400 mg daily for 18 days. The mean AUC of regorafenib increased by 33% and the mean AUC of M-2 and M-5 both decreased by 93%.

Effect of regorafenib on a substrate of UGT1A1 substrates: Eleven patients received irinotecan-containing combination chemotherapy with Stivarga at a dose of 160 mg. The mean AUC of irinotecan increased 28% and the mean AUC of SN-38 increased by 44% when irinotecan was administered 5 days after the last of 7 daily doses of Stivarga.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies examining the carcinogenic potential of regorafenib have not been conducted. Regorafenib itself did not demonstrate genotoxicity in *in vitro* or *in vivo* assays; however, a major human active metabolite of regorafenib, (M-2), was positive for clastogenicity, causing chromosome aberration in Chinese hamster V79 cells.

Dedicated studies to examine the effects of regorafenib on fertility have not been conducted; however, there were histological findings of tubular atrophy and degeneration in the testes, atrophy in the seminal vesicle, and cellular debris and oligospermia in the epididymides in male rats at doses similar to those in human at the clinical recommended dose based on AUC. In female rats, there were increased findings of necrotic corpora lutea in the ovaries at the same exposures. There were similar findings in dogs of both sexes in repeat dose studies at exposures approximately 83% of the human exposure at the recommended human dose based on AUC. These findings suggest that regorafenib may adversely affect fertility in humans.

13.2 Animal Toxicology and/or Pharmacology

In a chronic 26 week repeat dose study in rats there was a dose-dependent increase in the finding of thickening of the atrioventricular valve. At a dose that resulted in an exposure of approximately 12% of the human exposure at the recommended dose, this finding was present in half of the examined animals.

14 CLINICAL STUDIES

The clinical efficacy and safety of Stivarga were evaluated in an international, multi-center, randomized (2:1), double-blind, placebo-controlled trial (Study 1) in 760 patients with previously treated metastatic colorectal cancer. The major efficacy outcome measure was overall survival (OS); supportive efficacy outcome measures included progression-free survival (PFS) and objective tumor response rate.

Patients were randomized to receive 160 mg regorafenib orally once daily (n=505) plus Best Supportive Care (BSC) or placebo (n=255) plus BSC for the first 21 days of each 28-day cycle. Stivarga was administered with a low-fat breakfast that contains less than 30% fat [see *Dose and Administration (2.1), Clinical Pharmacology (12.3)*]. Treatment continued until disease progression or unacceptable toxicity.

In the all-randomized population, median age was 61 years, 61% were men, 78% were White, and all patients had baseline ECOG performance status of 0 or 1. The primary site of disease was colon (65%), rectum (29%), or both (6%). History of KRAS evaluation was reported for 729 (96%) patients; 430 (59%) of these patients were reported to have KRAS mutation. The median number of prior lines of therapy for metastatic disease was 3. All patients received prior

treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, and with bevacizumab. All but one patient with KRAS mutation-negative tumors received panitumumab or cetuximab.

The addition of Stivarga to BSC resulted in a statistically significant improvement in survival compared to placebo plus BSC (see Table 3 and Figure 1).

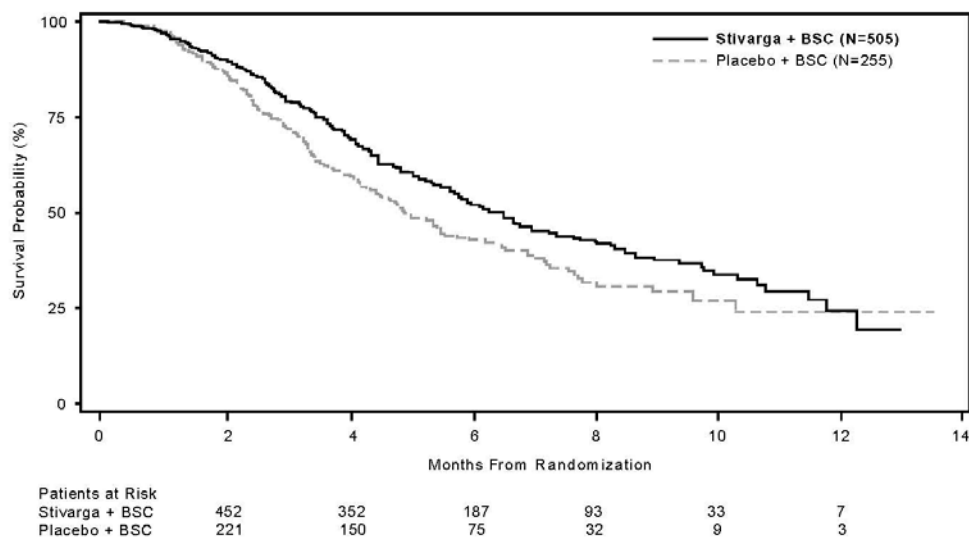
Table 3: Efficacy Results from Study 1

	Stivarga + BSC (N=505)	Placebo + BSC (N=255)
Overall Survival		
Number of deaths, n (%)	275 (55%)	157 (62%)
Median Overall Survival (months)	6.4	5.0
95% CI	(5.8, 7.3)	(4.4, 5.8)
HR (95% CI)	0.77 (0.64, 0.94)	
Stratified Log-Rank Test P-value ^{a,b}	0.0102	
Progression-free Survival		
Number of Death or Progression, n (%)	417 (83%)	231 (91%)
Median Progression-free Survival (months)	2.0	1.7
95% CI	(1.9, 2.3)	(1.7, 1.8)
HR (95% CI)	0.49 (0.42, 0.58)	
Stratified Log-Rank Test P-value ^a	<0.0001	
Overall Response Rate		
Overall response, n (%)	5 (1%)	1 (0.4%)
95% CI	0.3%, 2.3%	0%, 2.2%

^a Stratified by geographic region and time from diagnosis of metastatic disease.

^b Crossed the O'Brien-Fleming boundary (two-sided p-value < 0.018) at second interim analysis.

Figure 1: Kaplan-Meier Curves of Overall Survival



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Stivarga tablets are supplied in packages containing three bottles, with each bottle containing 28 tablets, for a total of 84 tablets per package (NDC 50419-171-03).

16.2 Storage and Handling

Store Stivarga at 25°C (77°F); excursions are permitted from 15 to 30°C (59 to 86°F) [See USP Controlled Room Temperature].

Store tablets in the original bottle and do not remove the desiccant. Keep the bottle tightly closed after first opening.

Discard any unused tablets 28 days after opening the bottle. Dispose of unused tablets in accordance with local requirements.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

Inform your patients of the following:

- Stivarga may cause severe or life-threatening liver damage. Inform patients that they will need to undergo monitoring for liver damage and to immediately report any signs or symptoms of severe liver damage to their health care provider.
- Stivarga can cause severe bleeding. Advise patients to contact their health care provider for any episode of bleeding.
- Stivarga can cause hand-foot skin reactions or rash elsewhere. Advise patients to contact their health care provider if they experience skin changes associated with redness, pain, blisters, bleeding, or swelling.
- Stivarga can cause or exacerbate existing hypertension. Advise patients they will need to undergo blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if symptoms from hypertension occur including severe headache, lightheadedness, or neurologic symptoms.
- Stivarga increased the risk for myocardial ischemia and infarction. Advise patients to seek immediate emergency help if they experience chest pain, shortness of breath, or feel dizzy or like passing out.
- Contact a healthcare provider immediately if they experience severe pains in their abdomen, persistent swelling of the abdomen, high fever, chills, nausea, vomiting, severe diarrhea (frequent or loose bowel movements), or dehydration.
- Stivarga may complicate wound healing. Advise patients to inform their health care provider if they plan to undergo a surgical procedure or had recent surgery.
- Inform patients that regorafenib can cause fetal harm. Advise women of reproductive potential and men of the need for effective contraception during Stivarga treatment and for up to 2 months after completion of treatment. Instruct women of reproductive potential to immediately contact her health care provider if pregnancy is suspected or confirmed during or within 2 months of completing treatment with Stivarga.
- Advise nursing mothers that it is not known whether regorafenib is present in breast milk and discuss whether to discontinue nursing or to discontinue regorafenib.
- Inform patients to take any missed dose on the same day, as soon as they remember, and that they must not take two doses on the same day to make up for a dose missed on the previous day.
- Inform patients to store medicine in the original container. Do not place medication in daily or weekly pill boxes. Any remaining tablets should be discarded 28 days after opening the bottle. Tightly close bottle after each opening and keep the desiccant in the bottle.

Patient Information
Stivarga (sti-VAR-gah)
(regorafenib)

tablets

Read this Patient Information before you start taking Stivarga and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about Stivarga?

Stivarga can cause serious side effects, including:

Liver problems. Stivarga can cause liver problems which can be serious and sometimes lead to death. Your healthcare provider will do blood tests to check your liver function before you start taking Stivarga and during your treatment with Stivarga to check for liver problems. Tell your healthcare provider right away if you get any of these symptoms of liver problems during treatment:

- yellowing of your skin or the white part of your eyes (jaundice)
- nausea or vomiting
- dark “tea-colored” urine
- change in sleep pattern

What is Stivarga?

Stivarga is a prescription medicine used to treat people with colon or rectal cancer that has spread to other parts of the body and for which they have received previous treatment with certain chemotherapy medicines.

Stivarga has not been used to treat children less than 18 years of age.

What should I tell my healthcare provider before taking Stivarga?

Before you take Stivarga, tell your healthcare provider if you:

- have liver problems
- have bleeding problems
- have high blood pressure
- have heart problems or chest pain
- plan to have any surgical procedures
- have any other medical conditions
- are pregnant or plan to become pregnant. Stivarga can harm your unborn baby. Females and males should use effective birth control during treatment with Stivarga and for 2 months after your last dose of Stivarga. Tell your healthcare provider right away if you or your partner becomes pregnant either while taking Stivarga or within 2 months after your last dose of Stivarga.
- are breastfeeding or plan to breastfeed. It is not known if Stivarga passes into your breast milk. You and your healthcare provider should decide if you will take Stivarga or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Stivarga may affect the way other medicines work, and other medicines may affect how Stivarga works.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take Stivarga?

- Take Stivarga exactly as your healthcare provider tells you.
- You will usually take Stivarga 1 time a day for 21 days (3 weeks) and then stop for 7 days (1 week). This is 1 cycle of treatment. Repeat this cycle for as long as your healthcare provider tells you to.
- Swallow Stivarga tablets whole.
- Take Stivarga at the same time each day with a low-fat breakfast. Examples of a low-fat breakfast include:
 - 2 slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly, and 8 ounces of skim milk (319 calories and 8.2 grams fat), **or**
 - 1 cup of cereal, 8 ounces of skim milk, 1 slice of toast with jelly, apple juice, and 1 cup of coffee or tea (520 calories and 2 grams fat).
- Your healthcare provider may stop your treatment or change the dose of your treatment if you get side effects.
- If you miss a dose, take it as soon as you remember on that day. Do not take two doses on the same day to make up for a missed dose.
- If you take too much Stivarga call your healthcare provider or go to the nearest emergency room right away.

What should I avoid while taking Stivarga?

- Avoid drinking grapefruit juice and taking St. John's Wort while taking Stivarga. These can affect the way Stivarga works.

What are the possible side effects of Stivarga?

Stivarga can cause serious side effects including:

- See "**What is the most important information I should know about Stivarga?**"
- **severe bleeding.** Stivarga can cause bleeding which can be serious and sometimes lead to death. Tell your healthcare provider if you have any signs of bleeding while taking Stivarga including:
 - vomiting blood or if your vomit looks like coffee-grounds
 - pink or brown urine
 - red or black (looks like tar) stools
 - coughing up blood or blood clots
 - menstrual bleeding that is heavier than normal
 - unusual vaginal bleeding
 - nose bleeds that happen often
- **a skin problem called hand-foot skin reaction and skin rash.** Hand-foot skin reactions can cause redness, pain, blisters, bleeding, or swelling on the palms of your hands or soles of your feet. If you get this side effect or a skin rash, your healthcare provider may stop your treatment for some time.
- **high blood pressure.** Your blood pressure should be checked every week for the first 6 weeks of starting Stivarga. Your blood pressure should be checked regularly and any high blood pressure should be treated while you are receiving Stivarga. Tell your healthcare provider if you have severe headaches, lightheadedness, or changes in your vision.
- **decreased blood flow to the heart and heart attack.** Get emergency help right away and call your healthcare provider if you get symptoms such as chest pain, shortness of breath, feel dizzy or feel like passing out.

- **a condition called Reversible Posterior Leukoencephalopathy Syndrome (RPLS).** Call your healthcare provider right away if you get: severe headaches, seizure, confusion, or change in vision.
- **a tear in your stomach or intestinal wall (perforation).** Tell your healthcare provider right away if you get:
 - severe pain in your stomach-area (abdomen)
 - swelling of the abdomen
 - high fever
- **wound healing problems.** If you need to have a surgical procedure, tell your healthcare provider that you are taking Stivarga. You should stop taking Stivarga at least 2 weeks before any planned surgery.

The most common side effects of Stivarga include:

- tiredness, weakness, fatigue
- loss of appetite
- frequent or loose bowel movements (diarrhea)
- swelling, pain and redness of the lining in your mouth, throat, stomach and bowel (mucositis)
- weight loss
- infection
- voice changes or hoarseness

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of Stivarga. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store Stivarga?

- Store Stivarga tablets at room temperature between 68° F to 77° F (20° C to 25° C).
- Keep Stivarga in the bottle that it comes in. Do not put Stivarga tablets in a daily or weekly pill box.
- The Stivarga bottle contains a desiccant to help keep your medicine dry. Keep the desiccant in the bottle.
- Keep the bottle of Stivarga tightly closed.
- Safely throw away (discard) any unused Stivarga tablets after 28 days of opening the bottle.

Keep Stivarga and all medicines out of the reach of children.

General information about Stivarga.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Stivarga for a condition for which it was not prescribed. Do not give Stivarga to other people even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about Stivarga. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Stivarga this is written for healthcare professionals.

For more information, go to www.STIVARGA-US.com or call 1-888-842-2937.

What are the ingredients in Stivarga?

Active ingredient: regorafenib

Inactive ingredients: cellulose microcrystalline, croscarmellose sodium, magnesium stearate, povidone and colloidal silicon dioxide.

Film coat: ferric oxide red, ferric oxide yellow, lecithin (soy), polyethylene glycol 3350, polyvinyl alcohol, talc and titanium dioxide.

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