STIVARGA- regorafenib tablet, film coated
Bayer HealthCare Pharmaceuticals Inc.

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, for oral use
Initial U.S. Approval: 2012

WARNING: HEPATOTOXICITY

See full prescribing information for complete boxed warning.

- **Severe and sometimes fatal hepatotoxicity has occurred in clinical trials. (5.1)**
- **Monitor hepatic function prior to and during treatment. (5.1)**
- **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)**

RECENT MAJOR CHANGES

Indications and Usage, Colorectal Cancer (1.1) 6/2016
Warnings and Precautions, Hepatotoxicity (5.1) 6/2016
Warnings and Precautions, Dermatologic Toxicity (5.3) 6/2016

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 RAS-wild type, an anti-EGFR therapy. (1.1)
- Locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate. (1.2)

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 a low-fat meal. (2.1, 12.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Hepatotoxicity: Monitor liver function tests and dose reduce or discontinue based on severity and duration.
- Hemorrhage: Permanently discontinue STIVARGA for severe or life-threatening hemorrhage. (5.2)
- Dermatologic 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 fistula: Discontinue STIVARGA. (5.7)
- Wound healing complications: Stop STIVARGA before surgery. Discontinue in patients with wound dehiscence. (5.8)
- Embryo-fetal toxicity: Can cause fetal harm. Advise women of potential risk to a fetus and to use effective contraception during treatment and for 2 months after the final dose. Advise males to use effective contraception for 2 months after the final dose. (5.9, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (≥20%) are asthenia/fatigue, hand-foot skin reaction (HFSR), diarrhea, decreased appetite/food intake, hypertension, mucositis, dysphonia, infection, pain, decreased weight, gastrointestinal and abdominal pain, rash, fever, and nausea. (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)
- BRCP substrates: Monitor patients closely for symptoms of increased exposure to BCRP substrates. (7.3)

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: 8/2016

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FULL PRESCRIBING INFORMATION

WARNING: HEPATOTOXICITY

- **Severe and sometimes fatal hepatotoxicity has occurred in clinical trials *[see Warnings and Precautions (5.1)]*.**
- **Monitor hepatic function prior to and during treatment *[see Warnings and Precautions (5.1)]*.**
- **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)]*.**

1 INDICATIONS AND USAGE

1.1 Colorectal Cancer

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 RAS wild-type, an anti-EGFR therapy.

1.2 Gastrointestinal Stromal Tumors

STIVARGA is indicated for the treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose is 160 mg STIVARGA (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 water after a low-fat meal that contains less than 600 calories and less than 30% fat *[see Clinical Pharmacology (12.3)]*. 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:

- 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 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 STIVARGA-treated patients in clinical trials. In most cases, liver dysfunction occurred within the first 2 months of therapy and was characterized by a hepatocellular pattern of injury.

In Study 1, fatal hepatic failure occurred in 1.6% of patients in the regorafenib arm and in 0.4% of patients in the placebo arm. In Study 2, fatal hepatic failure occurred in 0.8% of patients in the regorafenib arm *[see Adverse Reactions (6.1)]*.

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) and Use in Specific Populations (8.6)]*.

5.2 Hemorrhage

STIVARGA caused an increased incidence of hemorrhage. The overall incidence (Grades 1-5) was 21% and 11% in STIVARGA-treated patients compared to 8% and 3% in placebo-treated patients in Studies 1 and 2. Fatal hemorrhage occurred in 4 of 632 (0.6%) of STIVARGA-treated patients in Studies 1 and 2 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 Dermatologic Toxicity

STIVARGA increased the incidence of adverse reactions involving the skin and subcutaneous tissues (72% versus 24% in Study 1 and 78% versus 24% in Study 2), including hand-foot skin reaction (HFSR) also known as palmar-plantar erythrodysesthesia (PPE), and severe rash requiring dose modification.

The overall incidence of HFSR was higher in STIVARGA-treated patients, (45% versus 7% in Study 1 and 67% versus 12% in Study 2) than in the placebo-treated patients. Most cases of HFSR in STIVARGA-treated patients appeared during the first cycle of treatment (69% and 71% of patients who developed HFSR in Study 1 and Study 2, respectively). The incidence of Grade 3 HFSR (17% versus 0% in Study 1 and 22% versus 0% in Study 2), Grade 3 rash (6% versus <1% in Study 1 and 7% versus 0% in Study 2), serious adverse reactions of erythema multiforme (0.2% vs. 0% in Study 1) and Stevens-Johnson Syndrome (0.2% vs. 0% in Study 1) was higher in STIVARGA-treated patients *[see Adverse Reactions (6.1)]*. In both studies, a higher incidence of HFSR was observed in Asian patients treated with STIVARGA (all grades: 78.4% in Study 1 and 88.2% in Study 2 and Grade 3: 28.4% in Study 1 and 23.5% in Study 2) *[see Use in Specific Populations (8.8)]*.

Toxic epidermal necrolysis occurred in 0.17% of 1200 STIVARGA-treated patients across all clinical trials.

Withhold STIVARGA, reduce the dose, 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% versus 8% in Study 1 and 59% versus 27% in Study 2) *[see Adverse Reactions (6.1)]*. Hypertensive crisis occurred in 0.25% of 1200 STIVARGA-treated patients across all clinical trials. The onset of hypertension occurred during the first cycle of treatment in most patients who developed hypertension (72% in Study 1 and Study 2).

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 (2.2)]*.

5.5 Cardiac Ischemia and Infarction

STIVARGA increased the incidence of myocardial ischemia and infarction in Study 1 (1.2% versus 0.4%) *[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

Reversible posterior leukoencephalopathy syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in one of 1200 STIVARGA-treated patients across all clinical trials. Perform an evaluation for RPLS in any patient presenting with seizures, severe headache, visual disturbances, confusion or altered mental function. Discontinue STIVARGA in patients who develop RPLS.

5.7 Gastrointestinal Perforation or Fistula

Gastrointestinal perforation or fistula occurred in 0.6% of 1200 patients treated with STIVARGA across all clinical trials; this included four fatal events. In Study 2, 2.1% (4/188) of STIVARGA-treated patients who were treated during the blinded or open-label portion of the study developed gastrointestinal fistula or perforation; of these, two cases of gastrointestinal perforation were fatal. 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, discontinue treatment with regorafenib 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. Discontinue regorafenib in patients with wound dehiscence.

5.9 Embryo-Fetal Toxicity

Based on animal studies and its mechanism of action, STIVARGA can cause fetal harm when administered to a pregnant woman. There are no available data on STIVARGA use 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. Advise pregnant women of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment with STIVARGA and for 2 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with STIVARGA and for 2 months after the final dose *[see Use in Specific Populations (8.1), (8.3)]*.

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*)]*

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 most frequently observed adverse drug reactions (≥20%) in patients receiving STIVARGA are asthenia/fatigue, HFSR, diarrhea, decreased appetite/food intake, hypertension, mucositis, dysphonia, infection, pain, decreased weight, gastrointestinal and abdominal pain, rash, fever, and nausea.

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

6.1 Clinical Trials Experience

Colorectal Cancer

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 median duration of therapy was 7.3 (range 0.3, 47.0) weeks for patients receiving STIVARGA. Due to adverse reactions, 61% of the patients receiving STIVARGA required a dose interruption and 38% of the patients had their dose reduced. Adverse reactions that resulted in treatment discontinuation occurred in 8.2% of STIVARGA-treated patients compared to 1.2% of patients who received placebo. Hand-foot skin reaction (HFSR) and rash were the most common reasons for permanent discontinuation of STIVARGA.

Table 1 compares the incidence of adverse reactions (≥10%) in patients receiving STIVARGA and reported more commonly than in patients receiving placebo (Study 1).

Table 1: Adverse drug reactions reported in ≥10% of patients treated with STIVARGA in Study 1 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		
Pain	29	3	46	9
Fever	28	2	21	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

* Adverse reactions graded according to National Cancer Institute Common Toxicity for Adverse Events version 3.0 (NCI CTCAE v3.0).

† The term rash represents reports of events of drug eruption, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, papular rash, and pruritic rash.

‡ Fatal outcomes observed.

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

Table 2: Laboratory test abnormalities reported in Study 1

Laboratory Parameter	**STIVARGA (N=500 *)**			**Placebo (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.

Gastrointestinal Stromal Tumors

The safety data described below are derived from a randomized (2:1), double-blind, placebo-controlled trial (Study 2) in which 132 patients (median age 60 years; 64% men) with previously-treated GIST received STIVARGA as a single agent at a dose of 160 mg daily for the first 3 weeks of each 4 week treatment cycle and 66 patients (median age 61 years; 64% men) received placebo. The median duration of therapy was 22.9 (range 0.1, 50.9) weeks for patients receiving STIVARGA. Dose interruptions for adverse events were required in 58% of patients receiving STIVARGA and 50% of patients had their dose reduced. Adverse reactions that resulted in treatment discontinuation were reported in 2.3% of STIVARGA-treated patients compared to 1.5% of patients who received placebo.

Table 3 compares the incidence of adverse reactions (≥10%) in GIST patients receiving STIVARGA and reported more commonly than in patients receiving placebo (Study 2).

Table 3: Adverse reactions reported in ≥10% patients treated with STIVARGA in Study 2 and reported more commonly than in patients receiving placebo*

Adverse Reactions	**STIVARGA (N=132)**		**Placebo (N=66)**	
	Grade		**Grade**	
	All %	**≥ 3 %**	**All %**	**≥ 3 %**
Skin and subcutaneous tissue disorders				
HFSR/PPE	67	22	12	2
Rash †	30	7	3	0
Alopecia	24	2	2	0
General disorders				

and administration site conditions				
Asthenia/Fatigue	52	4	39	2
Fever	21	0	11	2
Vascular disorders				
Hypertension	59	28	27	5
Hemorrhage	11	4	3	0
Gastrointestinal disorders				
Diarrhea	47	8	9	0
Mucositis	40	2	8	2
Nausea	20	2	12	2
Vomiting	17	<1	8	0
Respiratory, thoracic and mediastinal disorders				
Dysphonia	39	0	9	0
Infections and infestations				
Infection	32	5	5	0
Metabolism and nutrition disorders				
Decreased appetite and food intake	31	<1	21	3
Hypothyroidism ‡	18	0	6	0
Nervous system disorders				
Headache	16	0	9	0
Investigations				
Weight loss	14	0	8	0

Musculoskeletal and connective tissue disorders				
Musculoskeletal stiffness	14	0	3	0

* Adverse reactions graded according to NCI CTCAE v4.0.

† The term rash represents reports of events of rash, erythematous rash, macular rash, maculo-papular rash, papular rash and pruritic rash.

‡ Hypothyroidism incidence based on subset of patients with normal TSH and no thyroid supplementation at baseline.

Laboratory abnormalities observed in Study 2 are shown in Table 4.

Table 4: Laboratory test abnormalities reported in Study 2

Laboratory Parameter	**STIVARGA (N=132*)**			**Placebo (N=66 *)**		
	Grade †			**Grade †**		
	All %	**3 %**	**4 %**	**All %**	**3 %**	**4 %**
Blood and lymphatic system disorders						
Thrombocytopenia	13	1	0	2	0	2
Neutropenia	16	2	0	12	3	0
Lymphopenia	30	8	0	24	3	0
Metabolism and nutrition disorders						
Hypocalcemia	17	2	0	5	0	0
Hypokalemia	21	3	0	3	0	0
Hypophosphatemia	55	20	2	3	2	0
Hepatobiliary disorders						
Hyperbilirubinemia	33	3	1	12	2	0
Increased AST	58	3	1	47	3	0
Increased ALT	39	4	1	39	2	0
Renal and urinary disorders						
Proteinuria	33	3	- ‡	30	3	- ‡
Investigations						
Increased lipase	14	0	1	5	0	0

* Percent based on number of patients with post-baseline samples which may be less than 132 (regorafenib) or 66 (placebo).

† NCI CTCAE v4.0.

‡ No Grade 4 denoted in NCI CTCAE v4.0.

6.2 Postmarketing Experience

The following adverse reaction has been identified during postapproval use of STIVARGA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to

reliably estimate their frequency or establish a causal relationship to drug exposure:

- hypersensitivity reaction

7 DRUG INTERACTIONS

7.1 Effect of Strong CYP3A4 Inducers on Regorafenib

Co-administration of a strong CYP3A4 inducer with STIVARGA decreased the plasma concentrations of regorafenib, increased the plasma concentrations of the active metabolite M-5, and resulted in no change in the plasma concentrations of the active metabolite M-2 *[see Clinical Pharmacology (12.3)]*, and may lead to decreased efficacy. Avoid concomitant use of STIVARGA with strong CYP3A4 inducers (e.g. rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort).

7.2 Effect of Strong CYP3A4 Inhibitors on Regorafenib

Co-administration of a strong CYP3A4 inhibitor with STIVARGA increased the plasma concentrations of regorafenib and decreased the plasma concentrations of the active metabolites M-2 and M-5 *[see Clinical Pharmacology (12.3)]*, and may lead to increased toxicity. Avoid concomitant use of STIVARGA with strong CYP3A4 inhibitors (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, and voriconazole).

7.3 Effect of Regorafenib on Breast Cancer Resistance Protein (BCRP) Substrates

Co-administration of STIVARGA with a BCRP substrate increased the plasma concentrations of the BCRP substrate *[see Clinical Pharmacology (12.3)]*. Monitor patients closely for signs and symptoms of exposure related toxicity to the BCRP substrate (e.g. methotrexate, fluvastatin, atorvastatin). Consult the concomitant BCRP substrate product information when considering administration of such products together with STIVARGA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal studies and its mechanism of action, STIVARGA can cause fetal harm when administered to a pregnant woman. There are no available data on STIVARGA use in pregnant women. Administration of 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 *[see Data]*. Advise pregnant women of the potential hazard to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4 % and 15 to 20%, respectively.

Data

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. Daily administration of regorafenib to pregnant rats during organogenesis resulted in fetal findings of delayed ossification at doses ≥ 0.8 mg/kg (approximately 5% of the recommended human dose based on body surface area) and 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.

8.2 Lactation

Risk Summary

There are no data on the presence of regorafenib or its metabolites in human milk, the effects of regorafenib on the breastfed infant, or on milk production. In rats, regorafenib and its metabolites are excreted in milk. Because of the potential for serious adverse reactions in breastfed infants from STIVARGA, do not breastfeed during treatment with STIVARGA and for 2 weeks after the final dose.

8.3 Females and Males of Reproductive Potential

Contraception

Females

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

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 2 months following the final dose of STIVARGA *[see Nonclinical Toxicology (13.1)]*.

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)]*.

8.4 Pediatric Use

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

Animal Data

In 28-day repeat-dose studies in rats there were dose-dependent findings of dentin alteration and angiectasis. These findings occurred 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 632 STIVARGA-treated patients enrolled in Studies 1 and 2, 37% were 65 years of age 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 dose adjustment is recommended in patients with mild or moderate hepatic impairment *[see Clinical Pharmacology (12.3)]*. 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), since it has not been studied in this population.

8.7 Renal Impairment

No dose adjustment is recommended for patients with mild, moderate, or severe renal impairment *[see Clinical Pharmacology (12.3)]*.

8.8 Race

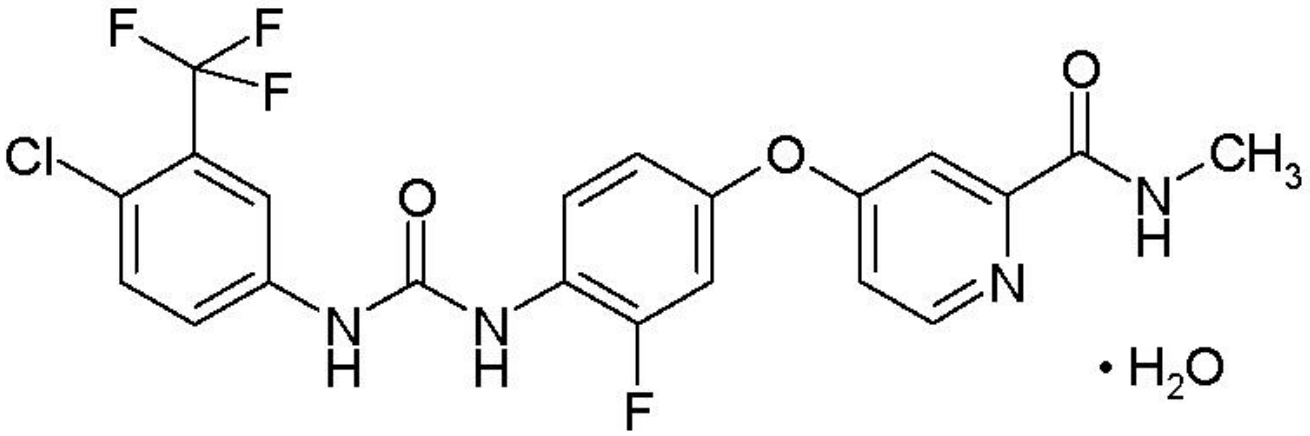
Based on pooled data from three placebo-controlled trials (Studies 1 and 2, and a study conducted in East Asia), a higher incidence of HFSR and liver function test abnormalities occurred in Asian patients treated with STIVARGA as compared with Whites *[see Warnings and Precautions (5.1, 5.3)]*. No starting dose adjustment is necessary based on race.

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 known 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-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, TrkA, 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.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of multiple doses of STIVARGA (160 mg once daily for 21 days) on the QTc interval was evaluated in an open-label, single-arm study in 25 patients with advanced solid tumors. No large changes in the mean QTc interval (i.e., > 20 msec) were detected in the study.

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 µg/mL at a median time of 4 hours and a geometric mean area under the plasma concentration vs. time curve (AUC) of 70.4 µg*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 µg/mL and a geometric mean AUC of 58.3 µg*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 Studies 1 and 2 *[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.

Elimination

Following a single 160 mg oral dose of STIVARGA, the geometric mean (minimum to maximum) 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 (minimum to maximum) elimination half-life of 51 hours (32 to 70 hours).

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 metabolites have 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).

Excretion

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.

Specific Populations

Age, sex, race and weight had no clinically meaningful effect on the pharmacokinetics of regorafenib.

Hepatic Impairment

The pharmacokinetics of regorafenib, M-2, and M-5 was 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).

Renal Impairment

The pharmacokinetics of regorafenib, M-2, and M-5 was evaluated in 6 patients with severe renal impairment (CLcr 15-29 mL/min) and 18 patients with normal/mild renal function (CLcr ≥60 mL/min) 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 severe renal impairment compared to patients with normal renal function. The pharmacokinetics of regorafenib has not been studied in patients with end-stage renal disease.

Drug Interaction Studies

Effect of Regorafenib on Cytochrome P450 Substrates: In vitro studies suggested that regorafenib is an inhibitor of CYP2C8, CYP2C9, CYP2B6, CYP3A4 and CYP2C19; M-2 is an inhibitor of CYP2C9, CYP2C8, CYP3A4 and CYP2D6, and M-5 is an inhibitor of CYP2C8. In vitro studies suggested that regorafenib is not an inducer of CYP1A2, CYP2B6, CYP2C19, and CYP3A4 enzyme activity.

Patients with advanced solid tumors received single oral doses of CYP substrates, 2 mg of midazolam (CYP3A4), 40 mg of omeprazole (CYP2C19) and 10 mg of warfarin (CYP2C9) or 4 mg of rosiglitazone (CYP2C8) one week before and two weeks after STIVARGA at a dose of 160 mg once daily. No clinically meaningful effect was observed in the mean AUC of rosiglitazone (N=12) or the mean omeprazole (N=11) plasma concentrations measured 6 hours after dosing or the mean AUC of midazolam (N=15). The mean AUC of warfarin (N=8) increased by 25% *[see Warnings and Precautions*

(5.2)].

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% *[see Drug Interactions (7.2)]*.

Effect of Neomycin on Regorafenib: Twenty-seven healthy men received a single 160 mg dose of STIVARGA and then 5 days after starting neomycin. Neomycin, a non-absorbable antibiotic, was administered at a dose of 1 gram three times daily for 5 days. No clinically meaningful effect on the mean AUC of regorafenib was observed; however, the mean AUC of M-2 decreased by 76% and the mean AUC of M-5 decreased by 86%. The decreased exposure of M-2 and M-5 may result in a decreased efficacy of STIVARGA. The effects of other antibiotics on the exposure of regorafenib and its active metabolites have not been studied.

Effect of Regorafenib on UGT1A1 Substrates: In vitro studies showed that regorafenib, M-2, and M-5 competitively inhibit UGT1A9 and UGT1A1 at therapeutically relevant concentrations. Eleven patients received irinotecan-containing combination chemotherapy with STIVARGA at a dose of 160 mg. The mean AUC of irinotecan increased by 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.

Effect of Regorafenib on BCRP Substrates: Administration of regorafenib (160 mg for 14 days) prior to administration of a single dose of rosuvastatin (5 mg), a BCRP substrate, resulted in a 3.8-fold increase in mean exposure (AUC) of rosuvastatin and a 4.6-fold increase in C_{max} *[see Drug Interactions (7.3)]*.

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

14.1 Colorectal Cancer

The clinical efficacy and safety of STIVARGA were evaluated in an international, multicenter, 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); additional 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 Dosage and Administration (2.1), Clinical Pharmacology (12.3)]*. Treatment continued until disease progression or unacceptable toxicity.

Baseline demographics were: median age 61 years, 61% men, 78% White, and all patients had an ECOG performance status of 0 or 1. The primary sites of disease were 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 5 and Figure 1).

Table 5: Efficacy Results from Study 1

	STIVARGA (N=505)	**Placebo (N=255)**
Overall Survival		
Number of Deaths (%)	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†,‡	0.0102	
Progression-Free Survival		
Number of Deaths or Progressions (%)	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†	<0.0001	
Overall Response Rate		
Overall Response, N (%)	5 (1%)	1 (0.4%)
95% CI	0.3%, 2.3%	0%, 2.2%

* CI=confidence interval

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

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

Figure 1: Kaplan-Meier Curves of Overall Survival

14.2 Gastrointestinal Stromal Tumors

The efficacy and safety of STIVARGA were evaluated in an international, multicenter, randomized (2:1), double-blind, placebo-controlled trial (Study 2) in 199 patients with unresectable, locally advanced or metastatic gastrointestinal stromal tumor (GIST), who had been previously treated with imatinib mesylate and sunitinib malate. Randomization was stratified by line of therapy (third vs. four or more) and geographic region (Asia vs. rest of the world).

The major efficacy outcome measure of Study 2 was progression-free survival (PFS) based on disease assessment by independent radiological review using modified RECIST 1.1 criteria, in which lymph nodes and bone lesions were not target lesions and progressively growing new tumor nodule within a pre-existing tumor mass was progression. The key secondary outcome measure was overall survival.

Patients were randomized to receive 160 mg regorafenib orally once daily (N=133) plus best supportive care (BSC) or placebo (N=66) plus BSC for the first 21 days of each 28-day cycle. Treatment continued until disease progression or unacceptable toxicity. In Study 2, the median age of patients was 60 years, 64% were men, 68% were White, and all patients had baseline ECOG performance status of 0 (55%) or 1 (45%). At the time of disease progression as assessed by central review, the study blind was broken and all patients were offered the opportunity to take STIVARGA at the investigator's discretion. Fifty-six (85%) patients randomized to placebo and 41 (31%) patients randomized to STIVARGA received open-label STIVARGA.

A statistically significant improvement in PFS was demonstrated among patients treated with STIVARGA compared to placebo (see Table 6 and Figure 2). There was no statistically significant difference in overall survival at the time of the planned interim analysis based on 29% of the total events for the final analysis.

Table 6: Efficacy Results for Study 2

	STIVARGA (N=133)	**Placebo (N=66)**
Progression-free Survival		
Number of deaths or progressions (%)	82 (62%)	63 (96%)
Median Progression-Free Survival (months)	4.8	0.9
95% CI	(3.9, 5.7)	(0.9, 1.1)
HR (95% CI)	0.27 (0.19, 0.39)	
Stratified log-rank test p-value*	<0.0001	
Overall Survival		
Number of Deaths (%)	29 (22%)	17 (26%)
Median Overall Survival (months)	NR†	NR†
HR (95% CI)	0.77 (0.42, 1.41)	
Stratified log-rank test p-value*,†	0.2	

* Stratified by line of treatment and geographical region.

† NR: Not reached.

Figure 2: Kaplan-Meier Curves of Progression-Free Survival for Study 2

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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 7 weeks after opening the bottle.Dispose of unused tablets in accordance with local requirements.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

Hepatotoxicity

Advise patients that they will need to undergo monitoring for liver damage and to report immediately any signs or symptoms of severe liver damage to their healthcare provider *[see Warnings and Precautions (5.1), Use in Specific Populations (8.8)]*.

Hemorrhage

Advise patients to contact their healthcare provider for unusual bleeding, bruising, or symptoms of bleeding, such as lightheadedness *[see Warnings and Precautions (5.2)].*

Dermatologic Toxicity

Advise patients to contact their healthcare provider if they experience skin changes associated with

redness, pain, blisters, bleeding, or swelling *[see Warnings and Precautions (5.3)].*

Hypertension

Advise patients they will need to undergo blood pressure monitoring and to contact their healthcare provider if blood pressure is elevated or if symptoms from hypertension occur including severe headache, lightheadedness, or neurologic symptoms *[see Warnings and Precautions (5.4)].*

Myocardial Ischemia and Infarction

Advise patients to seek immediate emergency help if they experience chest pain, shortness of breath, feel dizzy, or feel like passing out *[see Warnings and Precautions (5.5)]*.

Reversible posterior leukoencephalopathy syndrome

Advise patients to contact their healthcare provider if they experience signs and symptoms of RPLS *[see Warnings and Precautions (5.6)]*.

Gastrointestinal Perforation or Fistula

Advise patients to contact a healthcare provider immediately if they experience severe pains in their abdomen, persistent swelling of the abdomen, high fever, chills, nausea, vomiting , or dehydration *[see Warnings and Precautions (5.7)]*.

Wound Healing Complications

Advise patients to contact their healthcare provider if they plan to undergo a surgical procedure or had recent surgery *[see Warnings and Precautions (5.8)].*

Embryo-Fetal Toxicity

Advise patients that regorafenib can cause fetal harm. Advise a pregnant woman of the potential risk to a fetus *[see Warnings and Precautions (5.9), Use in Specific Populations (8.1, 8.3)]*.

Females and Males of Reproductive Potential

- Advise women of reproductive potential of the need for effective contraception during STIVARGA treatment and for 2 months after completion of treatment. Instruct women of reproductive potential to immediately contact her healthcare provider if pregnancy is suspected or confirmed during or within 2 months of completing treatment with STIVARGA *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1, 8.3)]*.
- Advise men of reproductive potential of the need for effective contraception during STIVARGA treatment and for 2 months after completion of treatment *[see Use in Specific Populations (8.3)]*.

Lactation

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 *[see Use in Specific Populations (8.2)]*.

Administration

- Advise patients to swallow the STIVARGA tablet whole with water at the same time each day with a low-fat meal. Inform patients that the low-fat meal should contain less than 600 calories and less than 30% fat *[see Dosage and Administration (2.1)]*.
- Advise patients to store medicine in the original container. Do not place medication in daily or weekly pill boxes. Discard any remaining tablets 7 weeks after opening the bottle. Tightly close bottle after each opening and keep the desiccant in the bottle *[see How Supplied/Storage and Handling (16.2)]*.

Missed dose

Advise 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.

Patient Package Insert

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

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
- a rare stomach, bowel, or esophagus cancer called GIST (gastrointestinal stromal tumors) that cannot be treated with surgery or that has spread to other parts of the body and for which they have received previous treatment with certain medicines

It is not known if Stivarga is safe and effective in 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 about all of your medical conditions, including if you:

- have liver problems
- have bleeding problems
- have high blood pressure
- have heart problems or chest pain
- plan to have any surgical procedures or have had recent surgery
- are pregnant or plan to become pregnant. Stivarga can harm your unborn baby.
    - Females should use effective birth control during treatment with Stivarga and for 2 months after your final dose of Stivarga. Tell your healthcare provider right away if you become pregnant during treatment with Stivarga or within 2 months after your final dose of Stivarga.
    - Males with female partners who can become pregnant should use effective birth control during treatment with Stivarga and for 2 months after your final dose of Stivarga.
- are breastfeeding or plan to breastfeed. It is not known if Stivarga passes into your breast milk. Do not breastfeed during treatment with Stivarga and for 2 weeks after your final dose of Stivarga.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter 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 with water after a low-fat meal.
- Take Stivarga at the same time each day with a low-fat meal that contains less than 600 calories and less than 30% fat.
- 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 during treatment with 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 during treatment with 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
- bruising
- lightheadedness
- **a skin problem called hand-foot skin reaction and severe skin rash**. Hand-foot skin reactions are common and sometimes can be severe. Tell your healthcare provider right away if you get redness, pain, blisters, bleeding, or swelling on the palms of your hands or soles of your feet, or a severe rash.
- **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 during treatment with 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 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, change in vision, or problems thinking.
- **a tear in your stomach or intestinal wall (bowel perforation).** Stivarga may cause a tear in your stomach or bowel perforation that can be serious and sometimes lead to death. Tell your healthcare provider right away if you get:
- severe pain in your stomach-area (abdomen)
- swelling of the abdomen
- high fever
- chills
- nausea
- vomiting
- dehydration
- **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
- frequent or loose bowel movements (diarrhea)
- loss of appetite
- swelling, pain and redness of the lining in your mouth, throat, stomach and bowel (mucositis)
- voice changes or hoarseness
- infection
- pain in other parts of your body
- weight loss
- stomach-area (abdomen) pain
- fever
- nausea

Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with Stivarga if you have certain side effects.
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 7 weeks of opening the bottle.

Keep Stivarga and all medicines out of the reach of children.
General information about the safe and effective use of 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. You can ask your healthcare provider or pharmacist for information about Stivarga that is written for health 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.

This Patient Information has been approved by the U.S. Food and Drug Administration. 6/2016

Manufactured in Germany

Manufactured for:

Bayer HealthCare Pharmaceuticals Inc.
Whippany, NJ 07981 USA

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Package/Label Display Panel

STIVARGA

regorafenib tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50419-171
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
REGORAFENIB MONOHYDRATE (UNII: MGN125FS9D) (REGORAFENIB - UNII:24T2A1DOYB)	REGORAFENIB	40 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	

MAGNESIUM STEARATE (UNII: 70097M6I30)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
LECITHIN, SOYBEAN (UNII: 1DI56QDM62)	
POLYETHYLENE GLYCOL 3350 (UNII: G2M7P15E5P)	
POLYVINYL ALCOHOL (UNII: 532B59J990)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POVIDONES (UNII: FZ989GH94E)	

Product Characteristics

Color	PINK (light)	**Score**	no score
Shape	OVAL	**Size**	16mm
Flavor		**Imprint Code**	BAYER
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50419-171-03	3 in 1 BOX	09/27/2012	
1	NDC:50419-171-01	28 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		
2	NDC:50419-171-00	210 in 1 BOX	09/27/2012	
2		28 in 1 BOTTLE; Type 0: Not a Combination Product		
3	NDC:50419-171-04	1 in 1 CARTON	09/27/2012	
3		28 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA203085	09/27/2012	

Labeler - Bayer HealthCare Pharmaceuticals Inc. (005436809)

Establishment

Name	Address	ID/FEI	Business Operations
Bayer Pharma AG		341081414	MANUFACTURE(50419-171)