Updated packaging to help accommodate dispensing needs

Manage dosing of STIVARGA® (regorafenib) for your previously treated mCRC patients' treatment plans[1,2]

Standard dosing and modifications
Dose escalation schedule as listed in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) (Category 2A)[3,4]*

Indication

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.

Important Safety Information

WARNING: HEPATOTOXICITY

- **Severe and sometimes fatal hepatotoxicity has occurred 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.**

Hepatotoxicity: Severe drug-induced liver injury with fatal outcome occurred in STIVARGA-treated patients across all 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 metastatic colorectal cancer (mCRC), fatal hepatic failure occurred in 1.6% of patients in the STIVARGA arm and in 0.4% of patients in the placebo arm.

mCRC=metastatic colorectal cancer.

*Category 2A: Based upon lower-level evidence, there is uniform National Comprehensive Cancer Network® (NCCN®) consensus that the intervention is appropriate.[3,4]

Please see additional Important Safety Information throughout this brochure. For important risk and use information, please click here for the full Prescribing Information, including the Boxed Warning.

Stivarga®
(regorafenib) tablets

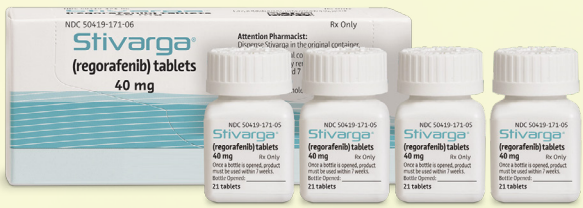
21-count bottles help accommodate dispensing of STIVARGA® (regorafenib)

On December 10, 2020, the FDA approved updated packaging for STIVARGA. Safety data, product storage, handling, and stability remain unchanged between the previous and updated packaging.

PREVIOUS PACKAGING
three 28-count bottles

Three bottles, each containing 28 tablets, for a total of 84 tablets per package[1,5]
(Box: NDC 50419-171-03) (Bottle: NDC 50419-171-01)

UPDATED PACKAGING
four 21-count bottles



Four bottles, each containing 21 tablets, for a total of 84 tablets per package[1,5]
(Box: NDC 50419-171-06) (Bottle: NDC 50419-171-05)

Each package includes a QR code that directs to stivarga-us.com

Important Safety Information (continued)

Liver Function Monitoring: Obtain liver function tests (ALT, AST, and bilirubin) before initiation of STIVARGA and monitor at least every 2 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 upper limit of normal (ULN) or baseline values. 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.

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Stivarga®
(regorafenib) tablets

Standard starting dose with options for dose management

STIVARGA® (regorafenib) dosing in the CORRECT, Phase III trial

The recommended starting dose is 160 mg STIVARGA (four 40-mg tablets) taken orally once daily for the first 3 weeks, followed by a 1-week treatment break.[1]

One cycle of STIVARGA treatment[1]

Week	1	2	3	4
Once-daily dose	 160 mg	 160 mg	 160 mg	Dosing-free interval

REPEAT EVERY MONTH

Dosage and administration for STIVARGA[1]

- Treatment should continue until disease progression or until unacceptable toxicity occurs
- STIVARGA should be taken whole with water after a low-fat meal that contains <600 calories and <30% fat at the same time each day
- Advise patients to take any missed dose on the same day, as soon as they remember, and that they must not take 2 doses on the same day to make up for a dose missed on the previous day
- No dose adjustment is recommended for patients with renal impairment
- The pharmacokinetics of STIVARGA have not been studied in patients who are on dialysis and there is no recommended dose for this patient population
- No dose adjustments are required based on mild (total bilirubin ≤upper limit of normal (ULN) and aspartate aminotransferase (AST) >ULN, or total bilirubin >ULN to ≤1.5x ULN) or moderate (total bilirubin >1.5 to ≤3x ULN and any AST) hepatic impairment. Closely monitor patients with hepatic impairment for adverse reactions. STIVARGA is not recommended for use in patients with severe hepatic impairment (total bilirubin >3x ULN), as STIVARGA has not been studied in this population

Follow up with your patients within the first 2 to 4 weeks of treatment[6,7]

Important Safety Information (continued)

Infections: STIVARGA caused an increased risk of infections. The overall incidence of infection (Grades 1-5) was higher (32% vs 17%) in 1142 STIVARGA-treated patients as compared to the control arm in randomized placebo-controlled trials. The incidence of grade 3 or greater infections in STIVARGA-treated patients was 9%. The most common infections were urinary tract infections (5.7%), nasopharyngitis (4.0%), mucocutaneous and systemic fungal infections (3.3%) and pneumonia (2.6%). Fatal outcomes caused by infection occurred more often in patients treated with STIVARGA (1.0%) as compared to patients receiving placebo (0.3%); the most common fatal infections were respiratory (0.6% vs 0.2%). Withhold STIVARGA for Grade 3 or 4 infections, or worsening infection of any grade. Resume STIVARGA at the same dose following resolution of infection.

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Stivarga® (regorafenib) tablets

Dose modifications with STIVARGA® (regorafenib) may help keep therapy manageable[1]

- If dose modifications are required, reduce the dose in 40-mg (1 tablet) increments
- The lowest recommended daily dose is 80 mg
- Resume STIVARGA at the same dose following resolution of infection

	Interrupt STIVARGA for the following	Reduce STIVARGA dose to 120 mg	Reduce STIVARGA dose to 80 mg	Discontinue STIVARGA permanently for the following
Hand-foot skin reaction (HFSR)	• Grade 2 HFSR that is recurrent or does not improve within 7 days despite dose reduction • Grade 3 HFSR (interrupt for a minimum of 7 days)	• First occurrence of Grade 2 HFSR of any duration • After recovery of Grade 3 HFSR	• Re-occurrence of Grade 2 HFSR at the 120-mg dose • After recovery of Grade 3 HFSR at 120-mg dose	• Failure to tolerate the 80-mg dose
Liver function test abnormalities	• Grade 3 aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevation	• Grade 3 AST/ALT elevation – only resume if the potential benefit outweighs the risk of hepatotoxicity		• Any occurrence of AST/ALT >20x upper limit of normal (ULN) • Any occurrence of AST/ALT >3x ULN with concurrent bilirubin >2x ULN • Re-occurrence of AST/ALT >5x ULN despite dose reduction to 120 mg
All other adverse reactions	• Symptomatic Grade 2 hypertension • Any Grade 3 or 4 adverse event (AE) • Worsening infection of any grade	• After recovery from any Grade 3 or 4 adverse reaction except infection	• After recovery from any Grade 3 or 4 adverse reaction at the 120-mg dose (except hepatotoxicity or infection)	• Failure to tolerate the 80-mg dose • Any Grade 4 AE (only resume if the potential benefit outweighs the risks)

Important Safety Information (continued)

Hemorrhage: STIVARGA caused an increased incidence of hemorrhage. The overall incidence (Grades 1-5) was 18.2% in 1142 patients treated with STIVARGA vs 9.5% with placebo in randomized, placebo-controlled trials. The incidence of grade 3 or greater hemorrhage in patients treated with STIVARGA was 3.0%. The incidence of fatal hemorrhagic events was 0.7%, involving the central nervous system or the respiratory, gastrointestinal, or genitourinary tracts. Permanently discontinue STIVARGA in patients with severe or life-threatening hemorrhage and monitor INR levels more frequently in patients receiving warfarin.

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Stivarga®
(regorafenib) tablets

NCCN Guidelines® include the following dose-escalation schedule (Category 2A)[3,4]*

Dose escalation is supported by the ReDOS clinical study[2†]

Regorafenib (STIVARGA®) dose escalation schedule in mCRC[2]

	Cycle 1				Cycle 2
Week	**1**	**2**	**3**	**4**	**1**
Once-daily dose	 80 mg	 120 mg	 160 mg	Dosing-free interval	Last dose from Cycle 1

*Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[3,4]

† The study supporting the dose-escalation schedule has not been reviewed by the FDA. The study was a randomized, phase II, US-based trial through the Academic and Community Cancer Research United (ACCRU) research network, which looked at the proportion of patients who completed 2 cycles of STIVARGA and initiated a third cycle (N=116). The efficacy of the alternative dosing schedule cannot be compared to the efficacy of other trials.[2]

- Dosing escalation takes place during the first 4-week cycle (3 weeks on, 1 week off)[3,4]
- Week 1: 80 mg of regorafenib (STIVARGA) (two 40-mg tablets) taken orally once daily, Week 2: 120 mg (three 40-mg tablets), Week 3 dose is 160 mg (four 40-mg tablets), followed by Week 4 dose-free interval[3,4]
- Subsequent cycles are dosed at the last dose from Cycle 1[3,4]

Important Safety Information (continued)

Gastrointestinal Perforation or Fistula: Gastrointestinal perforation occurred in 0.6% of 4518 patients treated with STIVARGA across all clinical trials of STIVARGA administered as a single agent; this included eight fatal events. Gastrointestinal fistula occurred in 0.8% of patients treated with STIVARGA and in 0.2% of patients in the placebo arm across randomized, placebo-controlled trials. Permanently discontinue STIVARGA in patients who develop gastrointestinal perforation or fistula.

Dermatological Toxicity: In randomized, placebo-controlled trials, adverse skin reactions occurred in 71.9% of patients with STIVARGA arm and 25.5% of patients in the placebo arm including hand-foot skin reaction (HFSR) also known as palmar-plantar erythrodysesthesia syndrome (PPES) and severe rash, requiring dose modification. In the randomized, placebo-controlled trials, the overall incidence of HFSR was higher in 1142 STIVARGA-treated patients (53% vs 8%) than in the placebo-treated patients. Most cases of HFSR in STIVARGA-treated patients appeared during the first cycle of treatment.

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Stivarga®
(regorafenib) tablets

STIVARGA® (regorafenib): Updated packaging to help support dispensing needs

Dispensing scenarios

	PRESCRIBED DOSE	Tablets per month*	Tablets per bottle	Bottles per month
Recommended starting dose	160 mg	84	21	4
If a patient's dosage is reduced to 120 mg	120 mg	63	21	3
If a patient's dosage is reduced to 80 mg	80 mg	42	21	2

*Based on 3 weeks of active treatment and 1-week treatment break.

For more information on the STIVARGA packaging update, contact a Bayer sales consultant or Bayer's Specialty Pharmacy team at 1-844-222-2937

Important Safety Information (continued)

Dermatological Toxicity (cont): The incidences of Grade 3 HFSR (16% vs <1%), Grade 3 rash (3% vs <1%), serious adverse reactions of erythema multiforme (<0.1% vs 0%), and Stevens-Johnson syndrome (<0.1% vs 0%) were higher in STIVARGA-treated patients. Across all trials, a higher incidence of HFSR was observed in Asian patients treated with STIVARGA (all grades: 72%; Grade 3: 18%). Toxic epidermal necrolysis occurred in 0.02% of 4518 STIVARGA-treated patients across all clinical trials of STIVARGA administered as a single agent. Withhold STIVARGA, reduce the dose, or permanently discontinue depending on the severity and persistence of dermatologic toxicity.

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Stivarga® (regorafenib) tablets

Important Safety Information (continued)

Hypertension: Hypertensive crisis occurred in 0.2% in STIVARGA-treated patients and in none of the patients in placebo arm across all randomized, placebo-controlled trials. STIVARGA caused an increased incidence of hypertension (30% vs 8% in mCRC). The onset of hypertension occurred during the first cycle of treatment in most patients who developed hypertension (67% in randomized, placebo controlled trials). 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.

Cardiac Ischemia and Infarction: STIVARGA increased the incidence of myocardial ischemia and infarction (0.9% with STIVARGA vs 0.2% with placebo) in randomized placebo-controlled trials. Withhold STIVARGA in patients who develop new or acute cardiac ischemia or infarction, and resume only after resolution of acute cardiac ischemic events if the potential benefits outweigh the risks of further cardiac ischemia.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Reversible posterior leukoencephalopathy syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristics finding on MRI, occurred in one of 4800 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.

Wound Healing Complications: Impaired wound healing complications can occur in patients who receive drugs that inhibit the VEGF signaling pathway. Therefore, STIVARGA has the potential to adversely affect wound healing. Withhold STIVARGA for at least 2 weeks prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of STIVARGA after resolution of wound healing complications has not been established.

Embryo-Fetal Toxicity: STIVARGA can cause fetal harm when administered to a pregnant woman. There are no available data on STIVARGA use in pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with STIVARGA and for 2 months after the final dose.

Nursing Mothers: 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.

Most Frequently Observed Adverse Drug Reactions in mCRC (≥30%): The most frequently observed adverse drug reactions (≥30%) in STIVARGA-treated patients vs placebo-treated patients in mCRC, respectively, were: asthenia/fatigue (64% vs 46%), pain (59% vs 48%), decreased appetite and food intake (47% vs 28%), HFSR/PPE (45% vs 7%), diarrhea (43% vs 17%), mucositis (33% vs 5%), weight loss (32% vs 10%), infection (31% vs 17%), hypertension (30% vs 8%), and dysphonia (30% vs 6%).

References: 1. STIVARGA [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc; December 2020. **2.** Bekaii-Saab TS, Ou F-S, Ahn DH, et al. Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study. *Lancet Oncol.* 2019;20(8):1070-1082. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon Cancer V.2.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed May 11, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. **4.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Rectal Cancer V.1.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed May 11, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. **5.** MedLibrary website. https://medlibrary.org/lib/rx/meds/stivarga/page/8/. Published December 9, 2020. Accessed May 24, 2021. **6.** Grothey A, George S, Van Cutsem E, et al. Optimizing treatment outcomes with regorafenib: personalized dosing and other strategies to support patient care. *Oncologist.* 2014;19:1-12. **7.** Krishnamoorthy SK, Relias V, Sebastian S, Jayaraman V, Wasif Saif M. Management of regorafenib-related toxicities: a review. *Therap Adv Gastroenterol.* 2015;8(5):285-297.

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Stivarga®
(regorafenib) tablets

ADDITIONAL SUPPORT WITH ACCESS SERVICES BY BAYER™

The power of patient support and expert assistance

$0 CO-PAY

NO monthly cap and up to $25,000 per year for privately insured patients. Annual enrollment is required.

- $0 co-pay for privately insured patients*
- NO monthly cap
- Covers 100% of co-pays up to $25,000 per year per patient

- Patients cannot participate if:
  - Prohibited by their insurance company or applicable laws
  - Enrolled in any type of government insurance or reimbursement program
- If Prior Authorization determinations are delayed or denied, patients will be assessed for temporary patient assistance

3 WAYS TO ENROLL IN $0 CO-PAY

1. Directly via www.zerocopaysupport.com or call 1-647-245-5622
2. Call Access Services by Bayer: 1-800-288-8374
3. Specialty Pharmacy Provider (SPP) Network

For more information, call us by phone: 1-800-288-8374

Nurse counselors: 9 AM-6 PM ET

A resource for patient education and support

- Answering questions, providing information, and offering patient assistance
- Education about potential AEs
- Patient educational materials/starter kits
- Refill reminders
- Outbound calls

Financial counselors: 9 AM-6 PM ET

A resource assisting with patient access

- Benefit verification, identification, and coordination of SPP
- $0 co-pay for privately insured patients*
- Alternative coverage research-referral to independent organizations that may assist qualified patients with their out-of-pocket expenses†

*Patients who are enrolled in any type of government insurance or reimbursement programs are not eligible. As a condition precedent of the co-payment support provided under this program, eg, co-pay refunds, participating patients and pharmacies are obligated to inform insurance companies and third-party payors of any benefits they receive and the value of this program and may not participate if this program is prohibited by or conflicts with their private insurance policy, as required by contract or otherwise. Void where prohibited by law, taxed, or restricted. Patients enrolled in Bayer's Patient Assistance Program are not eligible. Bayer may determine eligibility, monitor participation, equitably distribute product, and modify or discontinue any aspect of the Access Services by Bayer program at any time, including but not limited to this commercial co-pay assistance program.

†Patients do not automatically qualify for financial help from charitable organizations; eligibility criteria apply.

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