CHOOSE STIVARGA® (regorafenib) FOR YOUR 3L GIST PATIENTS

10+ YEARS OF STIVARGA CLINICAL EXPERIENCE COMPLEMENTED BY REAL-WORLD EVIDENCE (RWE)[1,2]

The only FDA-approved 3L treatment following imatinib and sunitinib in patients with gastrointestinal stromal tumor (GIST)[1,3]

Indication

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.

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.**

Please see additional Important Safety Information throughout this brochure and full Prescribing Information, including the Boxed Warning.

Stivarga® (regorafenib) tablets

ENTER

Upon clicking, this will take the user to the named section.

Stivarga® (regorafenib) tablets

NAVIGATING THE DATA

Stivarga® (regorafenib) tablets

TABLE OF CONTENTS
GRID TRIAL
GRID TRIAL SAFETY
STIVARGA RWE

STIVARGA® (regorafenib) significantly improved PFS in previously treated patients with GIST in the GRID trial

STUDY DESIGN

STIVARGA was studied in patients with a high unmet need following disease progression on 2 prior TKIs in the GRID trial.[4]

- GRID was a phase 3, randomized, placebo-controlled trial in 199 patients with metastatic or unresectable GIST who had progressed after failure with at least imatinib and sunitinib or after intolerance to imatinib with a primary endpoint of PFS, per modified RECIST 1.1[4]
- Secondary endpoints included OS, time to progression, ORR, and DCR (defined as rate of complete response or partial response plus stable disease lasting for ≥12 weeks)[4]

PFS

- 4.8-month (95% CI, 3.9-5.7) median PFS in the phase 3 GRID trial (vs 0.9 months [95% CI, 0.9-1.1] with placebo)[1,4]
- 73% reduction in risk of disease progression or death (HR: 0.27 [95% CI, 0.19-0.39]); *P*<0.0001[1,4]
- 82 of 133 STIVARGA patients (62%) vs 63 of 66 placebo patients (96%) experienced disease progression or died[1]
- 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[1]

OS

- Median OS was 17.4 months for both STIVARGA (95% CI, 14.9-20.2) and placebo (95% CI, 12.3-21.0) with HR: 0.91 (95% CI, 0.65-1.27) and *P* value* 0.5716[1]
- There was no statistically significant difference in OS at the final OS analysis, conducted at 162 OS events[1]
- 88% of patients in the placebo arm crossed over to open-label STIVARGA after disease progression[1]

DCR

- 52.6% DCR achieved for STIVARGA (70/133 patients) vs 9.1% for placebo (6/66 patients)[4]
  - DCR was a secondary endpoint[4]
  - DCR is defined as the rate of complete response or partial response plus stable disease lasting for ≥12 weeks[4]

LONG-TERM SAFETY FOLLOW-UP

- Of the 190 patients who received STIVARGA at any point during the GRID trial, 75 (39%) received STIVARGA for >1 year[5]

*A 2-sided *P* value by log-rank test stratified by line of treatment and geographical region.

CI=confidence interval; DCR=disease control rate; HR=hazard ratio; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors; TKI=tyrosine kinase inhibitor.

Important Safety Information (cont)

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 gastrointestinal stromal tumor (GIST), fatal hepatic failure occurred in 0.8% of patients in the STIVARGA arm.

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.

Please see additional Important Safety Information throughout this brochure and full Prescribing Information, including the Boxed Warning.

GLOBAL: Upon click this will continue to the previous page.
GLOBAL: Upon click this will open full prescribing information
GLOBAL: Upon click this will continue to the next page.

Stivarga® (regorafenib) tablets

TABLE OF CONTENTS
GRID TRIAL
GRID TRIAL SAFETY
STIVARGA RWE

Regular monitoring is critical for the management of AEs

Patients taking STIVARGA® (regorafenib) should be managed with frequent and proactive monitoring, especially during the first 2 to 4 weeks of treatment.[6,7]

Adverse drug reactions (≥10%) reported in patients treated with STIVARGA in GRID and reported more commonly than in patients receiving placebo.

AEs that resulted in treatment discontinuation were reported in 2.3% of STIVARGA-treated patients compared to 1.5% of patients who received placebo.[1]

Drug-related AEs occurring in ≥10% of patients treated with STIVARGA[1*]

AEs	STIVARGA (n=132) All grades	STIVARGA (n=132) Grade ≥3	Placebo (n=66) All grades	Placebo (n=66) Grade ≥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				
Pain	60%	8%	55%	14%
Diarrhea	47%	8%	9%	0%
Mucositis	40%	2%	8%	2%
Nausea	20%	2%	12%	2%
Vomiting	17%	<1%	8%	0%

AEs	STIVARGA (n=132) All grades	STIVARGA (n=132) Grade ≥3	Placebo (n=66) All grades	Placebo (n=66) Grade ≥3
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				
Muscle spasms	14%	0%	3%	0%

*AEs graded according to NCI CTCAE v4.0.
[†]The term rash represents reports of events of rash, erythematous rash, macular rash, maculopapular rash, papular rash, and pruritic rash.
[‡]Fatal outcomes observed.
[§]Hypothyroidism incidence based on subset of patients with normal TSH and no thyroid supplementation at baseline.

DOSING

- 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]
- In the GRID trial, 50% of patients receiving STIVARGA had their dose reduced, and dose interruptions for AEs were required in 58% of patients[1]
- For full Dosage and Administration information, please see the Prescribing Information

AE=adverse event; HFSR=hand-foot skin reaction; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PPE=palmar-plantar erythrodysesthesia; TSH=thyroid-stimulating hormone.

Important Safety Information (cont)

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%).

TABLE OF CONTENTS

GRID TRIAL

GRID TRIAL SAFETY

STIVARGA RWE

RWE complements data from randomized clinical trials. It is important to understand both the randomized clinical trial results and the limitations of retrospective real-world studies. Observational retrospective analyses are not intended for direct comparison with clinical trials.

STUDY DESIGN

The Call et al 2019 study was a retrospective analysis of the Life Raft Group (LRG) registry that included 1,716 GIST patients. The LRG registry is an international, internet-based, private, nonprofit medical research and patient advocacy organization.[2]

- The study included a retrospective analysis of the mOS and self-reported progression-free survival (srPFS) of GIST patients (n=107 patients who received 3L+ regorafenib) [2]
- mOS and srPFS estimates were determined using the Kaplan-Meier method and the log-rank test or the Gehan-Breslow-Wilcoxon test[2]
- Data were examined from 2000 to April 7, 2017[2]

LRG REGISTRY LIMITATIONS

- LRG registry members were self-referred[2]
- Low-risk patients were less likely to participate, and the LRG registry had a higher percentage of high-risk patients and patients with metastatic disease at diagnosis compared to population-based studies[2]
- Younger patients were more likely to be internet-/technology-savvy than older patients and thus more likely to participate in the registry[2]
- Proactive patients were more likely to participate in the registry as well as more likely to seek treatment from GIST expert centers and to participate in clinical trials[2]
- Lack of internet access, language barriers, and social/economic status were also likely barriers to participation[2]

mOS=median overall survival.

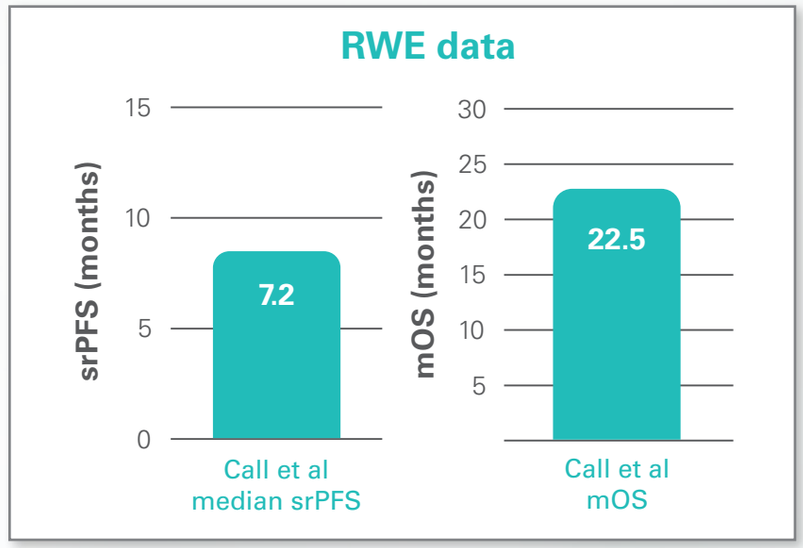
Important Safety Information (cont)

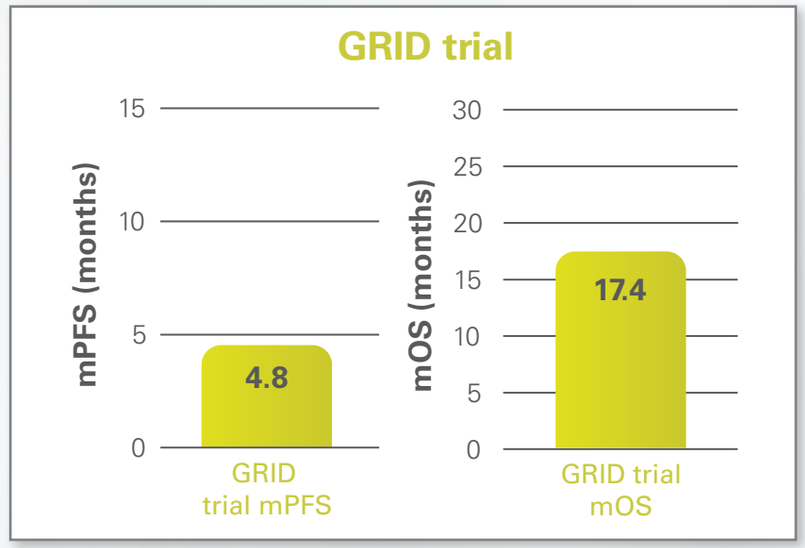
Infections (cont)

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.

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.

STIVARGA® (regorafenib) efficacy in RWE





STUDY LIMITATIONS

- This was a retrospective analysis of a long-term observational study, which may have missing or erroneous data entry and cannot determine causal relationships[2]
- The study examined patient-reported treatment and outcome data[2]
- Patients in 3L were not categorized by prior treatments; however, >98% of patients received imatinib in 1L, and 86% (452/526) of patients received sunitinib in 2L[2]
- The age range was 18 to 90 years[2]
- ECOG PS, dosing information, and safety data were not collected as part of the study

ECOG PS=Eastern Cooperative Oncology Group Performance Status; mPFS=median progression-free survival.

Important Safety Information (cont)

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. 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.

Choose STIVARGA® (regorafenib) for your 3L GIST patients

Stivarga® (regorafenib) tablets

NCCN Preferred Category 1

Regorafenib (STIVARGA®) remains the ONLY 3L approved treatment for patients with GIST[1,3]

National Comprehensive Cancer Network® (NCCN®) Guidelines recommend regorafenib as a category 1, systemic agent for patients with progressive, unresectable, or metastatic GIST after imatinib and sunitinib.[1,3]

Important Safety Information (cont)

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 (59% vs 27% in GIST). 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 GIST (≥30%): The most frequently observed adverse drug reactions (≥30%) in STIVARGA-treated patients vs placebo-treated patients in GIST, respectively, were: HFSR/PPE (67% vs 12%), pain (60% vs 55%), hypertension (59% vs 27%), asthenia/fatigue (52% vs 39%), diarrhea (47% vs 9%), mucositis (40% vs 8%), dysphonia (39% vs 9%), infection (32% vs 5%), decreased appetite and food intake (31% vs 21%), and rash (30% vs 3%).

References: 1. STIVARGA [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc; December 2020. **2.** Call JW, Wang Y, Montoya D, Scherzer NJ, Heinrich MC. Survival in advanced GIST has improved over time and correlates with increased access to post imatinib tyrosine kinase inhibitors: results from Life Raft Group Registry. *Clin Sarcoma Res*. 2019;9(4):1-14. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastrointestinal Stromal Tumors (GISTs). V1.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed June 15, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. **4.** Demetri GD, Reichardt P, Kang Y-K, et al; on behalf of the GRID Study Investigators. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):295-302. **5.** Demetri GD, Reichardt P, Kang Y-K, et al. Long-term safety of regorafenib (REG) in advanced gastrointestinal stromal tumors (GIST): updated safety data of the phase 3 GRID trial. *Annals of Oncology*. 2016; 27(suppl 6):vi483-vi492. **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(6):1. **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.

100 Bayer Boulevard, Whippany, NJ 07981 USA
Bayer, the Bayer Cross, and STIVARGA are registered trademarks of Bayer.
PP-STI-US-1856-1 12/23

Please see additional Important Safety Information throughout this brochure and full Prescribing Information, including the Boxed Warning.