Regorafenib: Drug information

(For additional information see "Regorafenib: Patient drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

ALERT: US Boxed 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 regorafenib for hepatotoxicity as manifested by elevated liver function tests (LFTs) or hepatocellular necrosis, depending upon severity and persistence.

Brand Names: US

Stivarga

Brand Names: Canada

Stivarga

Pharmacologic Category

Antineoplastic Agent, Tyrosine Kinase Inhibitor; Antineoplastic Agent, Vascular Endothelial Growth Factor (VEGF) Inhibitor

Dosing: Adult

Colorectal cancer, metastatic: Oral: 160 mg once daily for the first 21 days of each 28-day cycle; continue until disease progression or unacceptable toxicity (Grothey 2013)

Gastrointestinal stromal tumor (GIST), locally-advanced, unresectable, or metastatic: Oral: 160 mg once daily for the first 21 days of each 28-day cycle; continue until disease progression or unacceptable toxicity (Demetri 2013)

Hepatocellular carcinoma: Oral: 160 mg once daily for the first 21 days of a 28-day cycle; continue until disease progression or unacceptable toxicity (Bruix 2017)

Missed doses: Do not administer 2 doses on the same day to make up for a missed dose from the previous day.

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

CrCl ≥15 mL/minute: No dosage adjustment necessary.

ESRD on dialysis: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

Dosing: Hepatic Impairment

Preexisting mild (total bilirubin ≤ ULN and AST > ULN or total bilirubin > ULN to ≤1.5 times ULN) or moderate (total bilirubin >1.5 times to ≤3 times ULN and any AST) impairment: No dosage adjustment necessary; closely monitor for adverse effects.

Preexisting severe impairment (total bilirubin >3 times ULN): Use is not recommended (has not been studied).

Hepatotoxicity during treatment:

Grade 3 AST and/or ALT elevation: Withhold dose until recovery. If benefit of treatment outweighs toxicity risk, resume therapy at a reduced dose of 120 mg once daily.

AST or ALT >20 times ULN: Discontinue permanently.

AST or ALT >3 times ULN **and** bilirubin >2 times ULN: Discontinue permanently.

Recurrence of AST or ALT >5 times ULN despite dose reduction to 120 mg: Discontinue permanently.

Dosing: Adjustment for Toxicity

If dose reduction is necessary, reduce in 40 mg increments; the lowest recommended dose is 80 mg/day.

Dermatologic:

Grade 2 hand-foot skin reaction (HFSR; palmar-plantar erythrodysesthesia syndrome [PPES]) of any duration: Reduce dose to 120 mg once daily for first occurrence. If grade 2 HFSR recurs at this dose, further reduce the dose to 80 mg once daily. Interrupt therapy for grade 2 HFSR that is recurrent or fails to improve within 7 days in spite of dosage reduction.

Grade 3 HFSR: Interrupt therapy for a minimum of 7 days. Upon recovery, reduce dose to 120 mg once daily. If grade 2 to 3 toxicity recurs at this dose, further reduce dose to 80 mg once daily upon recovery. Interrupt therapy for grade 2 to 3 HFSR that is recurrent or fails to improve within 7 days in spite of dosage reduction.

Recurrent or persistent HFSR at 80 mg once daily: Discontinue treatment.

Other dermatologic toxicity: Withhold treatment, reduce dose or permanently discontinue treatment depending on the severity and persistence of the dermatologic toxicity. Symptomatic relief may be managed with supportive measures.

Hypertension: Grade 2 (symptomatic): Interrupt therapy.

Infection: Grade 3 or 4 (or worsening infection of any grade): Interrupt therapy; resume regorafenib at the same dose following infection resolution.

Other toxicity: Any grade 3 or 4 adverse reaction (other than hepatotoxicity or infection): Interrupt

therapy; upon recovery, reduce dose to 120 mg once daily (except infection). If any grade 3 or 4 adverse reaction occurs (other than hepatotoxicity or infection) while on this reduced dose, may further reduce dose to 80 mg once daily upon recovery. For any grade 4 adverse reaction, only resume therapy if the benefit outweighs the risk. Permanently discontinue therapy if unable to tolerate 80 mg once daily.

Gastrointestinal perforation/fistula: Discontinue permanently.

Hemorrhage (severe or life-threatening): Discontinue permanently.

Reversible posterior leukoencephalopathy syndrome (RPLS): Discontinue.

Wound dehiscence: Discontinue.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, Oral:

Stivarga: 40 mg [contains soybean lecithin]

Generic Equivalent Available (US) No

Prescribing and Access Restrictions Regorafenib is available only through the REACH support program. Information regarding program enrollment may be found at http://www.stivarga-us.com/hcp/mcrc/support.html or by calling 1-866-639-2827.

Administration Oral: Take at the same time each day. Swallow tablet whole with water after a low-fat meal (containing <600 calories and <30% fat).

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage. NIOSH recommends single gloving for administration of intact tablets or capsules (NIOSH 2016).

Use

Colorectal cancer, metastatic: Treatment of metastatic colorectal cancer in patients previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, anti-VEGF therapy, and anti-EGFR therapy (if *RAS* wild type)

Gastrointestinal stromal tumors: Treatment of locally-advanced, unresectable, or metastatic gastrointestinal stromal tumor (GIST) in patients previously treated with imatinib and sunitinib

Hepatocellular carcinoma: Treatment of hepatocellular carcinoma in patients previously treated with sorafenib

Medication Safety Issues

Sound-alike/look-alike issues:

Regorafenib may be confused with axitinib, crizotinib, dasatinib, erlotinib, imatinib, lapatinib, nilotinib, PAZOPanib, PONATinib, ramucirumab, ruxolitinib, sorafenib, sunitinib, vemurafenib

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Adverse Reactions

>10%:

Cardiovascular: Hypertension (30% to 59%)

Central nervous system: Fatigue (≤64%), pain (29% to 59%), voice disorder (18% to 39%), headache (10% to 16%)

Dermatologic: Palmar-plantar erythrodysesthesia (45% to 67%; more common in Asian patients), skin rash (26% to 30%), alopecia (7% to 24%)

Endocrine & metabolic: Hypophosphatemia (55% to 70%), hypocalcemia (17% to 59%), weight loss (13% to 32%), hypokalemia (21% to 31%), hyponatremia (30%), increased amylase (23% to 26%), hypothyroidism (6% to 18%)

Gastrointestinal: Gastrointestinal pain (60%), diarrhea (41% to 47%), decreased appetite (31% to 47%), increased serum lipase (14% to 46%), mucositis (13% to 40%), nausea (17% to 20%), vomiting (13% to 17%)

Hematologic & oncologic: Anemia (79%; grade 3: 5%; grade 4: 1%), lymphocytopenia (30% to 68%; grade 3: 8% to 16%; grade 4: 2%), thrombocytopenia (13% to 63%; grade 3: 1% to 5%; grade 4: <1%), increased INR (24% to 44%), hemorrhage (11% to 21%; grade ≥3: 2% to 5%), neutropenia (3% to 16%; grade 3: 1% to 3%)

Hepatic: Increased serum AST (58% to 93%), hyperbilirubinemia (33% to 78%), increased serum ALT (45% to 70%)

Infection: Infection (31% to 32%)

Neuromuscular & skeletal: Weakness (≤64%), stiffness (14%)

Renal: Proteinuria (33% to 84%)

Miscellaneous: Fever (20% to 28%)

1% to 10%:

Cardiovascular: Ischemic heart disease (≤1%), myocardial infarction (≤1%)

Dermatologic: Exfoliative dermatitis (1%)

Gastrointestinal: Mucocutaneous candidiasis (≤3%), pancreatitis (2%)

Genitourinary: Urinary tract infection (6%)

Hepatic: Hepatic failure (≤2%)

Infection: Candidiasis (≤3%)

Neuromuscular & skeletal: Muscle spasm (10%), tremor (1%)

Respiratory: Nasopharyngitis (4%), pneumonia (3%)

<1%, postmarketing, and/or case reports: Erythema multiforme, gastrointestinal fistula, gastrointestinal perforation, hepatic injury (severe), hypersensitivity reaction, hypertensive crisis, reversible posterior leukoencephalopathy syndrome (RPLS), Stevens-Johnson syndrome, toxic epidermal necrolysis

Contraindications

There are no contraindications listed in the manufacturer's US labeling.

Canadian labeling: Hypersensitivity to regorafenib, any component of the formulation, or sorafenib.

Warnings/Precautions

Concerns related to adverse effects:

• Cardiovascular events: Myocardial ischemia and infarction were observed at a higher incidence than placebo in a clinical trial. Interrupt therapy in patients who develop new or acute onset ischemia or infarction; resume only if the benefit of therapy outweighs the cardiovascular risk.

• Dermatologic toxicity: Skin reactions occurred commonly, including hand-foot skin reaction (HFSR), also known as palmar-plantar erythrodysesthesia syndrome (PPES), and severe rash requiring dose reduction. Grade 3 or 4 HFSR was observed more frequently in regorafenib-treated patients (compared to placebo), and although rare, erythema multiforme and Stevens Johnson syndrome were also observed more frequently in regorafenib-treated patients. Toxic epidermal necrolysis has also been reported (rare). Onset of HFSR typically occurs in the first cycle of treatment. Therapy interruptions, dosage reductions, and/or discontinuation may be necessary depending on the severity and persistence. Supportive treatment may be of benefit for symptomatic relief. Pooled data from several clinical trials showed a higher incidence of HFSR in Asian patients compared to Caucasians.

In addition to recommended dosage modifications, the following treatments may be used for management of HFSR (McLellan 2015): A manicure/pedicure to remove hyperkeratotic areas/calluses which may predispose to HFSR and mechanical support/correction for abnormal weight bearing prior to treatment are recommended. During treatment, patients should use alcohol-free moisturizers liberally, reduce exposure to hot water (may exacerbate hand-foot symptoms), avoid constrictive footwear and excessive skin friction, and avoid vigorous exercise/activities that may stress hands or feet. Patients should wear thick cotton gloves/socks and wear shoes with padded insoles. Grade 1 HFSR may be relieved with moisturizing creams, cotton gloves and socks (at night) and/or keratolytic creams such as urea (10% to 40%) or salicylic acid (6%) along with a topical analgesic (eg, lidocaine gel) to relieve pain. Apply topical steroid (eg, clobetasol ointment or foam) twice daily to erythematous areas of grade 2 HFSR (in addition to continuing grade 1 management); topical analgesics and then systemic analgesics (if appropriate) may be used for pain control; dose reduction may be necessary. Grade 3 HFSR should be

managed by continuing grades 1 and 2 symptomatic management and interrupting treatment for at least 7 days until resolved to grade 1 or lower.

• Gastrointestinal perforation: Gastrointestinal perforation or fistula has occurred in a small number of patients treated with regorafenib; some cases were fatal. Monitor for signs/symptoms of perforation (fever, abdominal pain with constipation, and/or nausea/vomiting); permanently discontinue if perforation or fistula develop.

• Hemorrhage: The incidence of hemorrhage was increased with regorafenib. Hemorrhage of the respiratory, gastrointestinal, or genitourinary tracts was observed in trials; some cases were fatal. Permanently discontinue in patients who experience severe or life-threatening bleeding. In patients receiving concomitant warfarin, monitor INR frequently.

• Hepatotoxicity: **[US Boxed Warning]: Severe and sometimes fatal hepatotoxicity has been observed in clinical trials. Monitor hepatic function at baseline and during treatment. Interrupt therapy for hepatotoxicity; dose reductions or discontinuation are necessary depending on the severity and persistence.** Hepatic dysfunction, characterized by a hepatocellular injury pattern, typically occurred with the first 2 months of treatment in clinical trials. Closely monitor in patients with mild or moderate impairment for adverse events; use is not recommended in severe impairment. A higher incidence of hepatotoxicity has been observed in Asian patients (particularly Japanese), compared to Caucasians (Li 2015).

• Hypersensitivity: Hypersensitivity reactions have been observed with regorafenib.

• Hypertension: Elevated blood pressure was observed in clinical trials (onset typically in the first cycle of therapy); ensure blood pressure is adequately controlled prior to initiation. Monitor blood pressure weekly for the first 6 weeks and monthly thereafter or as clinically indicated; if hypertension develops, interrupt therapy or permanently discontinue for severe or uncontrolled hypertension. Hypertensive crisis has occurred in some patients. Patients 65 years and older had an increased incidence of grade 3 or higher hypertension (compared to younger patients).

• Infection: An increased rate of infection (including fatal events) was observed in regorafenib-treated patients in clinical trials. The most commonly reported infections were urinary tract infections, nasopharyngitis, mucocutaneous and systemic fungal infections, and pneumonia. Respiratory infections were the most commonly reported fatal infections. Interrupt therapy for grade 3 or 4 infections (or worsening infection of any grade).

• Reversible posterior leukoencephalopathy syndrome (RPLS): RPLS occurred very rarely in regorafenib-treated patients; evaluate promptly if symptoms (eg, seizures, severe headache, visual disturbances, confusion or altered mental function) occur. Discontinue if diagnosis is confirmed.

• Wound healing impairment: Regorafenib inhibits vascular endothelial growth factor, which may lead to impaired wound healing. Discontinue regorafenib at least 2 weeks prior to scheduled surgery; resume regorafenib postsurgery based on clinical judgment of wound healing; discontinue if wound dehiscence occurs.

Concurrent drug therapy issues:

• Drug-drug/drug-food interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

Special populations:

• Asian patients: A higher incidence of hepatotoxicity and hand-foot skin reactions were observed in Asian patients, particularly in Japanese patients, compared to non-Asian patients (Li 2015).

Metabolism/Transport Effects

Substrate of CYP3A4 (major), UGT1A9; **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; **Inhibits** BCRP/ABCG2, UGT1A1, UGT1A9

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Aprepitant: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

BCRP/ABCG2 Substrates: Regorafenib may increase the serum concentration of BCRP/ABCG2 Substrates. *Risk C: Monitor therapy*

Beta-Blockers: Regorafenib may enhance the bradycardic effect of Beta-Blockers. *Risk C: Monitor therapy*

Bisphosphonate Derivatives: Angiogenesis Inhibitors (Systemic) may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Specifically, the risk for osteonecrosis of the jaw may be increased. *Risk C: Monitor therapy*

Bosentan: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Calcium Channel Blockers (Nondihydropyridine): Regorafenib may enhance the bradycardic effect of Calcium Channel Blockers (Nondihydropyridine). *Risk C: Monitor therapy*

Conivaptan: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk X: Avoid combination*

CYP3A4 Inducers (Moderate): May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May decrease the serum concentration of Regorafenib. *Risk X: Avoid combination*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Regorafenib. *Risk X: Avoid combination*

Dabrafenib: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Management: Seek alternatives to the CYP3A4 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk*

C: Monitor therapy

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Digoxin: Regorafenib may enhance the bradycardic effect of Digoxin. *Risk C: Monitor therapy*

Fosaprepitant: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk X: Avoid combination*

Grapefruit Juice: May increase the serum concentration of Regorafenib. *Risk X: Avoid combination*

Idelalisib: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk X: Avoid combination*

Irinotecan Products: UGT1A1 Inhibitors may increase serum concentrations of the active metabolite(s) of Irinotecan Products. Specifically, concentrations of SN-38 may be increased. UGT1A1 Inhibitors may increase the serum concentration of Irinotecan Products. *Risk X: Avoid combination*

Ivabradine: Regorafenib may enhance the bradycardic effect of Ivabradine. *Risk C: Monitor therapy*

Neomycin: May decrease serum concentrations of the active metabolite(s) of Regorafenib. *Risk C: Monitor therapy*

Netupitant: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

Palbociclib: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

PAZOPanib: BCRP/ABCG2 Inhibitors may increase the serum concentration of PAZOPanib. *Risk X: Avoid combination*

Pitolisant: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). Management: Combined use of pitolisant with a CYP3A4 substrate that has a narrow therapeutic index should be avoided. Other CYP3A4 substrates should be monitored more closely when used with pitolisant. *Risk D: Consider therapy modification*

Sarilumab: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Siltuximab: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Simeprevir: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). *Risk C: Monitor therapy*

St John's Wort: May decrease the serum concentration of Regorafenib. *Risk X: Avoid combination*

Stiripentol: May increase the serum concentration of CYP3A4 Substrates (High risk with Inhibitors). Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any

CYP3A4 substrate used with stiripentol requires closer monitoring. *Risk D: Consider therapy modification*

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates (High risk with Inducers). *Risk C: Monitor therapy*

Topotecan: BCRP/ABCG2 Inhibitors may increase the serum concentration of Topotecan. *Risk D: Consider therapy modification*

Warfarin: May enhance the adverse/toxic effect of Regorafenib. Specifically, the risk for bleeding may be increased. *Risk C: Monitor therapy*

Food Interactions Regorafenib serum concentrations may be altered when taken with grapefruit or grapefruit juice. Management: Avoid concurrent use.

Pregnancy Implications In animal reproduction studies, teratogenic effects were observed with doses less than the equivalent human dose. Based on animal reproduction studies and on the mechanism of action, regorafenib may cause fetal harm if administered during pregnancy. Patients (male and female) should use effective contraception during therapy and for at least 2 months following treatment.

Breast-Feeding Considerations It is not known if regorafenib is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during treatment and for 2 weeks after the last dose.

Dietary Considerations Avoid grapefruit juice.

Monitoring Parameters Obtain liver function tests at baseline, every 2 weeks during the first 2 months of treatment, then monthly or more frequently if clinically necessary (weekly until improvement if liver function tests are elevated). CBC with differential and platelets and serum electrolytes (baseline and periodic). Monitor INR more frequently if receiving warfarin. Monitor blood pressure weekly for the first 6 weeks of therapy and with every subsequent cycle, or more frequently if indicated. Monitor for hand-foot skin reaction (HFSR)/palmar-plantar erythrodysesthesia syndrome (PPES); it is recommended to monitor for signs of HFSR during the first weeks of treatment, then every 1 to 2 weeks for 2 cycles, then every 4 to 6 weeks thereafter (McLellan 2015). Monitor for signs/symptoms of cardiac ischemia or infarction, bleeding, GI perforation or fistula, infection, and reversible posterior leukoencephalopathy syndrome (severe headaches, seizure, confusion, or change in vision). Monitor for impaired wound healing.

Mechanism of Action Regorafenib is a multikinase inhibitor; it targets kinases involved with tumor angiogenesis, oncogenesis, and maintenance of the tumor microenvironment which results in inhibition of tumor growth. Specifically, it inhibits VEGF receptors 1-3, KIT, PDGFR-alpha, PDGFR-beta, RET, FGFR1 and 2, TIE2, DDR2, TrkA, Eph2A, RAF-1. BRAF, $BRAF^{V600E}$, SAPK2, PTK5, and Abl.

Pharmacodynamics/Kinetics

Absorption: A high-fat meal increased the mean AUC of the parent drug by 48% compared to the fasted state and decreased the mean AUC of the M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl) active metabolites by 20% and 51%, respectively. A low-fat meal increased the mean AUC of regorafenib, M-2, and M-5 by 36%, 40% and 23%, respectively (as compared to the fasted state).

Protein binding: 99.5% (active metabolites M-2 and M-5 are also highly protein bound)

Metabolism: Hepatic via CYP3A4 and UGT1A9, primarily to active metabolites M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl)

Bioavailability: Tablets: 69%; Oral solution: 83%

Half-life elimination: Regorafenib: 28 hours (range: 14 to 58 hours); M-2 metabolite: 25 hours (range: 14 to 32 hours); M-5 metabolite: 51 hours (range: 32 to 70 hours)

Time to peak: 4 hours

Excretion: Feces (71%; 47% as parent compound; 24% as metabolites); Urine (19%)

Pricing: US

Tablets (Stivarga Oral)

40 mg (28): $5952.60

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

Brand Names: International

Stivar (UA); Stivarga (AE, AR, AT, AU, BE, CH, CL, CY, CZ, DE, DK, EC, EE, ES, FI, FR, GB, HK, HR, HU, IE, IL, IS, JO, JP, KR, LB, LT, LU, LV, MT, MY, NL, NO, NZ, PE, PH, PL, PT, QA, RO, SA, SE, SG, SI, SK, TH, TR)

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