Drug Monograph

A - Drug Name

regorafenib

COMMON TRADE NAME(S): Stivarga®

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B - Mechanism of Action and Pharmacokinetics

Regorafenib is an inhibitor of multiple protein kinases, including those involved in tumor angiogenesis (VEGFR1, 2, 3, TIE2), oncogenesis (KIT, RET, RAF1, BRAF, BRAFV600E), metastasis (VEGFR3, PDGFR, FGFR) and tumour immunity (CSFIR).

Absorption	Bioavailability	70-83%
	Effects with food	Exposure to regorafenib and its major metabolites is highest when taken with a low-fat (< 30% fat) meal as compared to either fasting or a high-fat (~50% fat) meal.
Distribution	PPB	99.5% (similar for regorafenib and its metabolites)
Metabolism	Main enzymes involved	CYP3A4, glucuronidation by UGT1A9
	Active metabolites	M-2 (N-oxide) & M-5 (N-oxide and N-desmethyl)
	Inhibitor of	UGT1A1 and UGT1A9 (clinical significance unknown), BCRP, Pgp

Elimination	Half-life	20-30 hours for regorafenib and M-2, 40-100 hours for M-5
	Feces	71% of dose
	Urine	19% of dose

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C - Indications and Status

Health Canada Approvals:

- Colorectal cancer
- Gastrointestinal stromal tumors (GIST)
- Hepatocellular carcinoma (HCC)

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

The following adverse effects are from a phase 3 study for metastatic colorectal cancer, where incidence is higher in the treatment arm than placebo arm.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (3%)	I E
	Arterial thromboembolism (1%)	E
	Artery aneurysm (rare)	E D L
	Artery dissection (rare)	E D L
	Cardiotoxicity (1%)	E D
	Hypertension (30%) (arterial; may be severe)	I E
	QT interval prolonged (rare)	E
Dermatological	Alopecia (8%)	D

	Hand-foot syndrome (47%) (may be severe)	E
	Rash (26%) (may be severe, including SJS, TEN, etc)	E
Gastrointestinal	Anorexia, weight loss (47%)	E D
	Diarrhea (43%)	E
	Gastrointestinal fistula or perforation (1%)	E
	Mucositis (18%)	E
General	Delayed wound healing	E
	Fatigue (64%)	E
	Fever (28%)	E
	Pain (59%)	E
Hematological	Anemia (6%) (severe)	E
	Disseminated intravascular coagulation (rare)	E
	Hemorrhage (21%) (GU, GI, respiratory; may be severe)	E
	INR / prothrombin time abnormal (4%) (severe)	E
	Thrombocytopenia (3%) (severe)	E
Hepatobiliary	↑ Amylase / lipase (46%)	E
	Cholecystitis (2%)	E
	↑ LFTs (65%) (may be severe)	E
Infection	Infection (31%) (may be severe)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (59%) (Ca, K, Na, PO4; 31% severe)	E
	Hypothyroidism (4%)	D
Musculoskeletal	Other (14%) (musculoskeletal stiffness)	E
Neoplastic	Secondary malignancy (Keratocanthoma/squamous cell carcinoma) (rare)	D
Nervous System	Dysgeusia (8%)	I E
	Headache (10%)	E
	Posterior reversible encephalopathy syndrome (PRES) (rare)	E
Renal	Proteinuria (9%)	E
	Renal failure (1%)	D
Respiratory	Dysphonia (30%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for regorafenib include ↑ LTFs, fatigue, abnormal electrolyte(s), pain, anorexia, weight loss, hand-foot syndrome, ↑ amylase / lipase, diarrhea, infection and dysphonia.

Onset of **hypertension** occurred usually during the first cycle. Rare occurrences of hypertensive crisis have been reported.

Severe cases of **artery dissection** (with or without hypertension) and **artery aneurysm** (including rupture) have been reported in patients using VEGFR TKIs.

Fatal cases of **GI perforation**, **hepatobiliary disorders**, **infection** and **hemorrhage** have been observed

Prevention of **hand-foot syndrome** (HFS) includes control of calluses and minimizing pressure stress to soles and palms. Management may include the use of keratolytic creams (e.g. urea, salicylic acid, or alpha hydroxyl acid-based creams applied sparingly only on hyperkeratotic areas) and moisturizing creams (applied liberally) for symptomatic relief. Dose modification or interruption is required in severe, persistent cases (refer to Dosing section).

Rare severe **skin reactions** have been reported in clinical studies and post-market, including Steven-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).

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E - Dosing

Refer to protocol by which the patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Hypertension should be controlled before initiating therapy.

Regorafenib should be stopped at least 2 weeks before scheduled surgery as it may suppress wound healing.

Adults:

Q4week cycle:

Oral: 160 mg once daily for 3 weeks followed by 1 week off therapy

Dosage with Toxicity:

Dose Level	Regorafenib Dose
0	160 mg
-1	120 mg
-2	80 mg
If further dose reduction indicated or > 4 week hold for toxicity	Discontinue

Dosage with toxicity:

Toxicity	Grade	Action
Hand-foot syndrome	2	For 1st occurrence continue therapy with ↓1 dose level. If not ≤ grade 1 within 7 days, hold drug until ≤ grade 1. If recurs, hold until ≤ grade 1 and ↓ 1 dose level
	3	Hold for ≥7 days until Grade ≤1, ↓ 1 dose level
Hypertension	2 or 3	Start / increase antihypertensive. If symptomatic, hold until controlled, otherwise continue regorafenib. If cannot control with antihypertensives, ↓ 1 dose level
	4	Discontinue
Hepatotoxicity (AST/ALT)	2	If bilirubin < 2 x ULN - ↓ 1 dose level; If bilirubin ≥ 2 x ULN - discontinue
	3	If bilirubin < 2 x ULN, discontinue; if must continue (i.e. benefit > risk) - hold until AST/ALT ≤ grade 1 or baseline then ↓ 1 dose level; if recurs → discontinue. If bilirubin ≥ 2 x ULN - discontinue
	4	Discontinue
Pneumonitis	Any grade	Hold and investigate. If confirmed, discontinue
Cardiac ischemia		Hold; consider discontinuing
GI perforation or fistula, arterial thromboembolism, RPLS, wound dehiscence, severe hemorrhage, severe	Any grade	Discontinue

dermatologic reaction (SJS/TEN), intolerance of 80mg dose level		
Other toxicity	3	Hold until ≤ grade 1 then ↓ 1 dose level
	4	Discontinue; if benefit > risk and regorafenib must be restarted, reduce by 1 dose level

Dosage with Hepatic Impairment:

Patients with mild and moderate hepatic impairment experienced a higher incidence of adverse events than patients with normal hepatic function at baseline.

Hepatic Impairment	Regorafenib Dose
Mild (Child-Pugh A)	No change; monitor closely
Moderate (Child-Pugh B)	No change; monitor closely
Severe (Child-Pugh C)	Avoid use; no data

Dosage with Renal Impairment:

CrCl (mL/min)	Regorafenib Dose
≥ 60	No change
30 - 59	No change; monitor closely
15 - 29	No change; monitor closely
< 15 or ESRD	No data

Dosage in the elderly:

No dose adjustments are required. No differences in safety or efficacy were observed between older and younger patients.

Dosage based on gender:

Female patients have higher overall incidence of adverse effects as compared to males (50% vs 40%).

Dosage based on ethnicity:

Several studies suggest similar exposure in various Asian populations (Chinese, Japanese, Korean) as in Caucasians. A higher incidence of HFS, severe liver function test abnormalities and hepatic dysfunction was observed in clinical trials in Asian (Japanese in particular) patients as compared with Caucasians. Severe liver injury with fatal outcome was reported in 1.5% of Japanese patients as compared with <0.1% in non-Japanese patients.

Children:

Regorafenib should not be used in children or adolescents as efficacy and safety in patients aged less than 18 have not been established. Abnormalities in dentition, epiphyseal hypertrophy, and adverse effects in the reproductive system have been documented in juvenile animal studies.

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F - Administration Guidelines

- Swallow tablets whole with a glass of water, after a low-fat (<30% fat) and low-calorie (~300-550 calories) meal. Example meal: 2 slices of white toast with 1 tablespoon of low-fat margarine, 1 tablespoon of jelly and 8 ounces of skim milk (~319 calories and 8.2 grams of fat)
- Take the dose at the same time each day.
- A missed dose should be taken as soon as remembered on the same day. Otherwise, skip this and take the next dose on the following day. Do not take two doses on the same day.
- Store tablets in their original container at 15-30°C.
- Do not remove desiccant from bottle and keep tightly closed. Protect from moisture.
- Discard the tablets after the bottle has been opened for 7 weeks.

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G - Special Precautions

Contraindications:

- Regorafenib is contraindicated in patients who have a hypersensitivity to this drug or any of its components, to sorafenib, or to any drugs in the same class

Other Warnings/Precautions:

- Blood pressure should be controlled before initiating regorafenib.
- Stop regorafenib at least 2 weeks before scheduled surgery as it may suppress wound healing.
- Exercise caution in patients with ischemic heart disease, low baseline heart rate (< 60 bpm), history of syncope or arrhythmia, sick sinus syndrome, SA block, AV block, CHF or on concomitant medications that decrease heart rate.
- Patients on warfarin should be monitored closely due to increased risk of bleeding.
- Mild hyperbilirubinemia may occur in patients with Gilbert's syndrome.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: Unlikely
- Clastogenicity: Yes
- Embryotoxicity: Documented in animals
- Teratogenicity: Documented in animals
  Regorafenib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **8 weeks** after the last dose
- Excretion into breast milk: Documented in animals
  Breastfeeding is not recommended during treatment and for **2 weeks** after the last dose.
- Fertility effects: Documented in animals

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H - Interactions

Concurrent administration of regorafenib with CYP 2C8, 2C9, 3A4 and 2C19 substrates is unlikely to result in clinically significant drug interactions.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ exposure to regorafenib (± 33%) and ↓ exposure to M-2 and M-5 (± 94%)	↓ metabolism of regorafenib	Avoid concomitant administration with strong CYP3A4 inhibitors
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ exposure to regorafenib (50%) and ↑ exposure to M-5 (3-4 fold)	↑ metabolism of regorafenib	Avoid concomitant administration with strong CYP3A4 inducers
Drugs that result in bradycardia	↑ risk of bradycardia	Additive	Avoid if possible
BCRP substrates (i.e. methotrexate, fluvastatin, atorvastatin, rosuvastatin)	↑ exposure to BCRP substrates	Regorafenib is a BCRP inhibitor	Caution; monitor for substrate toxicity
UGT1A1 and 1A9 substrates (e.g. irinotecan)	↑ exposure to substrate and/or its metabolites	Regorafenib and M-2 are UGT1A1/9 inhibitors, M-5 is a UGT1A1 inhibitor	Caution; monitor closely as clinical significance unknown
Antibiotics	Effect unclear	↓ enterohepatic circulation	Caution

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Blood pressure	Baseline and weekly for the first 6 weeks of therapy, then prior to every cycle or more often if required
Liver function tests (ALT, AST, bilirubin)	Baseline and at least every 2 weeks during the first 2 months of therapy then at least monthly and as clinically indicated
Renal function tests	Baseline and before each cycle
Electrolytes (including phosphate, calcium, sodium, potassium), ECG	Baseline and as clinically indicated (especially in patients at risk of developing QT prolongation)
Thyroid function tests	Baseline and as clinically indicated
Clinical toxicity assessment for rash, fatigue, hand-foot syndrome, cardiovascular or GI effects, bleeding, neurologic or pulmonary symptoms	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
INR	More frequently in patients receiving warfarin

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- regorafenib - For the treatment of metastatic and/or unresectable gastrointestinal stromal tumors (GIST) in patients who have had disease progression on, or intolerance to, imatinib and sunitinib, according to specific criteria ()
- regorafenib - For the treatment of unresectable, advanced hepatocellular carcinoma (HCC) according to clinical criteria

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K - References

Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017 Jan 07;389(10064):56-66.

Demetri GD, Reichardt P, Kang YK, et al. 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.

Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:303-12.

Prescribing Information: Stivarga® (regorafenib). Bayer Inc. February 2013 and December 2020.

Product Monograph: Stivarga® (regorafenib). Bayer Inc., March 2020.

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August 2023 Modified Indications, Adverse effects, Dosage in renal impairment, Pregnancy/breastfeeding, Interactions and Monitoring sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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