DRUG NAME: Regorafenib

SYNONYM(S)[1]: BAY 73-4506, regorafenib monohydrate[2]

COMMON TRADE NAME(S): STIVARGA®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Regorafenib is a multiple receptor tyrosine kinase (RTK) inhibitor. RTKs are involved in cell proliferation, cell survival and tumour progression, depending on the specific kinase.[3] Regorafenib and/or its active metabolites (M-2, M-5) inhibit kinases involved in tumour angiogenesis (VEGFR-1, VEGFR-2, VEGFR-3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E), and maintenance of tumour microenvironment (PDGFR, FGFR).[1,2]

PHARMACOKINETICS:

Oral Absorption	bioavailability 70-83%; C_{max} 3-4 h; fat content in meals results in variable exposure, optimal plasma levels achieved after a low-fat, low-calorie meal (<30% fat, ~300-550 calories)	
Distribution	multiple peak concentrations at 4, 8, and 24 h post-daily dosing due to enterohepatic circulation of drug and metabolites	
	cross blood brain barrier?	no information found
	volume of distribution	88 L
	plasma protein binding	99.5% (regorafenib), 99.8% (M-2), 99.95% (M-5)
Metabolism	primarily in the liver by oxidation (CYP 3A4) and glucuronidation (UGT 1A9)	
	active metabolite(s)	M-2 (N-oxide), M-5 (N-oxide and N-desmethyl)
	inactive metabolite(s)	none specified
Excretion	metabolites may be reduced or hydrolyzed in the GI tract by microbial flora and allow for reabsorption of unconjugated drug and metabolites (enterohepatic circulation)	
	urine	19%
	feces	71% (47% as parent compound, 24% as metabolites)
	terminal half life	20-30 h (regorafenib and M-2), 40-100 h (M-5)
	clearance	no information found

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:
*Colorectal cancer
*Gastrointestinal stromal tumour (GIST)
*Liver cancer

Other uses:
Osteosarcoma[4]

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to regorafenib or sorafenib[2]
- pregnant women and women at risk of becoming pregnant[2]

Caution:
- ***impaired wound healing*** has been associated with vascular endothelial growth factor (VEGF) inhibitors; stop regorafenib at least 2 weeks prior to surgery and re-initiate post-surgery based on clinical assessment of the wound site[2]
- ***cardiac adverse events*** **(**including arrhythmias, congestive heart failure, and myocardial ischemia) have been reported with regorafenib; use with caution in patients at risk for or who have a history of cardiac events, including those who are bradycardic, have a history of arrhythmia, or are taking heart rate lowering drugs[2]
- ***hypertension*** has been observed with regorafenib; hypertension should be well controlled prior to starting treatment[2]

Special populations:
- ***Asian*** patients have reported a higher incidence of hand-foot skin reaction[2]
- patients with ***hepatic impairment*** may have a higher incidence of adverse events compared to patients with normal baseline hepatic function[2]
- ***female*** patients have reported a higher overall incidence of serious adverse events compared to male patients[2]
- patients who are ***65 years or older*** have reported a higher incidence of severe hypertensive events[2]
- safety and efficacy in ***pediatric*** patients has not been established; studies in animals showed hypertrophy in epiphyseal growth plates, abnormalities in teeth/bones/cartilage, and adverse effects on the reproductive system were more pronounced in juvenile animals[5]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test and in mammalian *in vitro* and *in vivo* mutation tests. M-2 metabolite is clastogenic in a mammalian *in vitro* chromosome test.[2]

Fertility: In animal studies, reported findings included atrophy/degeneration of seminiferous tubules, oligospermia, aspermia, and a reduced number of corpora lutea and developing follicles. The observed changes were reported at exposures below the anticipated human exposure and were only partially reversible.[5]

Pregnancy: In animal studies, the incidence of cardiovascular, genitourinary, and skeletal malformations was increased and regorafenib was considered embryolethal and teratogenic at exposures below the anticipated human exposure. Regorafenib should not be used during pregnancy and patients of reproductive potential should use contraception during treatment and for at least 8 weeks after the last dose.[5]

Breastfeeding is not recommended due to the potential secretion into human breast milk. In animal studies, regorafenib and metabolites were excreted in milk of lactating study subjects.[2,3]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[6,7] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.[8,9]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (5%, severe 1-2%)[8]
	thrombocytopenia (6-15%, severe 1-3%)
cardiac	***cardiac adverse events*** (3-9%, severe 1%); see paragraph following **Side Effects** table
endocrine	hypothyroidism (13%)
gastrointestinal	*emetogenic potential:* low[10]
	constipation (15%, severe 1%)[9]
	diarrhea (34-47%, severe 1-8%)[2,8]
	gastrointestinal perforation or ***fistula*** (2%); permanently discontinue treatment
	nausea (20%, severe 2%)
	stomatitis/mucosal inflammation (16-38%, severe 1-3%)[2,8,9]
	vomiting (17%, severe <1%)
general disorders and administration site conditions	***asthenia/fatigue*** (39-64%, severe 1-15%)[2,9]
	fever (10-28%, severe 1-2%)[2,8]
	myalgia (14%, severe 1%)[9]
	pain (29%, severe 1-2%)
hepatobiliary	***hepatobiliary disorders*** (20%, severe 2%); see paragraph following **Side Effects** table
infections and infestations	***infection*** (31-32%, severe 1-7%)
investigations	hyperbilirubinemia (9-19%, severe 1-6%)[2,8]
	increased lipase (6%)
	increased transaminases (11%, severe 3%)
	weight loss (14-32%, severe <1%)
metabolism and nutrition	***decreased appetite*** (21-47%, severe 1-5%)[2,9]
	hypocalcemia (6%)
	hypokalemia (8%)
	hypophosphatemia (5-6%)
musculoskeletal and connective tissue	musculoskeletal stiffness (14%)
nervous system	dysgeusia (7-10%)[2,8]
	dysphonia (11-39%, severe <1%)[2,8,9]
	headache (16%)
	reversible posterior leukoencephalopathy syndrome; see paragraph following **Side Effects** table
renal and urinary	proteinuria (7-8%, severe 1%)[2,8]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
respiratory, thoracic and mediastinal	epistaxis (2-6%)[5]; see paragraph following **Side Effects** table
skin and subcutaneous tissue	alopecia (7-24%, severe 2%)[2,8]
	dry skin (5-9%)[2,8]
	erythema multiforme, Stevens-Johnson Syndrome (<1%)
	hand-foot skin reaction (47-67%, severe 17-22%); see paragraph following **Side Effects** table
	rash (18-30%, severe 2-7%)
vascular	***hemorrhage*** (5-21%, severe 1-2%)[2,8]; see paragraph following **Side Effects** table
	hypertension (28-59%, severe 1-2%)[2,8]; see paragraph following **Side Effects** table

Adapted from standard reference[2] unless specified otherwise.

Cardiac adverse events, including myocardial ischemia and/or infarction, have been associated with regorafenib. Use with caution in patients with a history of ischemic heart disease. For new or acute onset cardiac ischemia and/or infarction, hold regorafenib until resolution; reinitiate therapy only after consideration of potential benefits and risks. Permanently discontinue therapy if there is no resolution of symptoms.[2]

Hypertension usually occurs in the first cycle of treatment. Blood pressure should be controlled prior to starting treatment. Monitor blood pressure weekly for the first 6 weeks of treatment and regularly thereafter as indicated. Hypertension may be treated with a combination of standard anti-hypertensive therapy and regorafenib dose reduction or interruption. Discontinue regorafenib for hypertensive crisis or severe/persistent hypertension despite anti-hypertensive therapy.[2]

Hand-foot skin reaction (HFSR) has been reported with an incidence of 47-67%. Management of HFSR may include symptomatic and supportive measures,[3] dose reduction, or interruption of regorafenib. In severe or persistent cases despite dose reductions, permanently discontinue regorafenib.[1,2]

Hemorrhagic events involving the respiratory, genitourinary, and gastrointestinal tracts have been reported with regorafenib and are sometimes fatal. However, most bleeding events are grade 1 or 2 in severity. Regoragenib may interact with warfarin; therefore patients on warfarin should be closely monitored. Discontinue regorafenib in patients with severe or life threatening hemorrhage.[5]

Abnormal ***liver function tests*** and ***hepatic dysfunction*** with fatal outcomes have been reported with regorafenib. Dose reduction or interruption of regorafenib may be required. Permanently discontinue regorafenib if patient develops[2]:

- AST or ALT greater than 20 times the upper limit of normal (grade 4),
- AST or ALT greater than 3 times the upper limit of normal with concurrent bilirubin greater than 2 times the upper limit of normal, or
- re-occurrence of AST or ALT greater than 5 times the upper limit of normal (grade 3) despite dose reduction.

Reversible posterior leukoencephalopathy syndrome (RPLS), a rare neurologic disorder, has been reported with regorafenib. Symptoms may include seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Brain imaging is necessary to confirm diagnosis. Discontinue regorafenib when signs/symptoms of RPLS are present and provide supportive management. The safety of reinitiating treatment with regorafenib is not known.[2]

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INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
5-fluorouracil[3]	regorafenib does not affect 5-fluorouracil pharmacokinetics		
irinotecan[2]	irinotecan exposure increased by 28%; SN-38 metabolite AUC increased by 44%	regorafenib inhibition of glucuronidation via UGT1A1 and UGT1A9	clinical significance is unknown; monitor for increased irinotecan adverse effects
ketoconazole[2]	regorafenib AUC increased by 33%; exposure of metabolites decreased by 94% (M-2) and 93% (M-5)	ketoconazole inhibition of CYP 3A4	avoid concurrent use with strong CYP 3A4 inhibitors
midazolam[2]	midazolam AUC increased by 12% and C_{max} increased by 28%	regorafenib inhibition of CYP 3A4	not considered clinically significant; action not required
omeprazole[2]	regorafenib does not affect omeprazole exposure		
oxaliplatin[3]	oxaliplatin AUC increased by 39%	regorafenib inhibition of glucuronidation via UGT1A1 and UGT1A9	clinical significance is unknown; monitor for increased oxaliplatin adverse effects
rifampin[2]	regorafenib AUC decreased by 50%; M-5 metabolite exposure increased by 3-4 times. No change in M-2 metabolite.	rifampin induction of CYP 3A4	avoid concurrent use with strong CYP 3A4 inducers
rosiglitazone[2]	regorafenib does not affect rosiglitazone exposure		
warfarin[5]	S-warfarin AUC increased by 25% and C_{max} increased by 26%	regorafenib inhibition of CYP 2C9 (weak)	monitor INR regularly; watch for increased bleeding

Grapefruit and grapefruit juice may inhibit CYP 3A4 metabolism of regorafenib in the intestinal wall and theoretically increase regorafenib plasma levels and reduce exposure for its metabolites; clinical significance is unknown.[1]

Regorafenib undergoes enterohepatic circulation. Concurrent use with antibiotics which disrupt the gastrointestinal tract flora and affect enterohepatic circulation of regorafenib may alter regorafenib exposure; clinical significance is unknown.[2]

SUPPLY AND STORAGE:

Oral: Bayer Inc. supplies regorafenib as 40 mg film-coated tablets. Store at room temperature in original container. Keep bottle tightly closed after opening and do not remove the desiccant.[2]

Additional information: Once bottle is opened, discard remaining tablets after 7 weeks.[5]

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DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Oral:	Cycle Length: ***4 weeks***[2,14,15]***:***	***160 mg*** (range 80 -160 mg) PO ***once daily*** for 21 consecutive days starting on day 1 (total dose per cycle 3360 mg [range 1680-3360 mg]) Round dose to the nearest 40 mg. Administer at the same time each day after a light, low-fat, low-calorie meal (<30% fat, ~300-550 calories).
Concurrent radiation:	no information found	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"	
Dosage in renal failure:	mild to severe impairment: no adjustment required[16] end-stage renal disease: no information found	
Dosage in hepatic failure:	mild to moderate impairment: no adjustment required[2]; however, the incidence of adverse reactions is reported to increase with any degree of hepatic impairment[16] severe impairment: no information found	
Dosage in dialysis:	no information found	

Children: not recommended for use in children and adolescents[2]

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