Regimen Monograph

A - Regimen Name

REGO Regimen

Regorafenib

Disease Site

Gastrointestinal
- Gastrointestinal Stromal Tumours

Sarcoma
- GIST

Intent

Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

Treatment of adult patients with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) who have had disease progression on or intolerance to imatinib and sunitinib treatment

Supplementary Public Funding

regorafenib

Exceptional Access Program (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) (EAP Website)

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B - Drug Regimen

regorafenib	160 mg	PO	Days 1 to 21

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal – No routine prophylaxis; PRN recommended

- Also refer to CCO Antiemetic Recommendations.

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

Other Supportive Care:

- 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. (Also refer to dose modifications section.)

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Hypertension should be controlled before initiating therapy.

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

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

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 dermtaologic reaction (SJS/TEN), severe hemorrhage, intolerance of 80mg dose level	Any grade	Discontinue
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

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

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 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.

Dosage in the Elderly

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

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F - Adverse Effects

Refer to regorafenib drug monograph(s) for additional details of adverse effects.

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• ↑ LFTs (may be severe) • Fatigue • Electrolyte abnormalities	• Anorexia, weight loss • Hand-foot syndrome • ↑ amylase/lipase • Diarrhea • Myelosuppression ± infection • Arterial hypertension (may be severe) • Dysphonia • Pain • Rash (may be severe)	• Hemorrhage (may be severe) • Mucositis • Musculoskeletal stiffness • Headache	• Cardiotoxicity • Arrhythmia, QT prolonged • Arterial thromboembolism • Artery aneurysm / dissection • GI fistula or perforation • Delayed wound healing • Cholecystitis • DIC • RPLS/PRES • Renal failure • Squamous cell carcinoma

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G - Interactions

Refer to regorafenib drug monograph(s) for additional details

- Regorafenib is metabolized by CYP3A4; avoid concomitant administration with strong CYP3A4 inhibitors or inducers.
- Avoid concurrent use of drugs that can result in bradycardia if possible.
- Regorafenib inhibits BCRP and may increase the exposure to BCRP substrates (e.g. methotrexate, fluvastatin, atorvastatin, rosuvastatin); monitor for substrate toxicity.
- Regorafenib and its active metabolites are inhibitors of UGT1A1 and UGT1A9; they can increase exposure to substrates of these enzymes (e.g. irinotecan); monitor for toxicity.

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H - Drug Administration and Special Precautions

Refer to regorafenib drug monograph(s) for additional details.

Administration:

- Swallow tablets whole with a glass of water, after a low-fat (<30% fat) and low-calorie (~300-550 calories) meal.
- 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 dose 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 15-30ºC.
- 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.

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 (<60bpm), 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.

Pregnancy and Lactation:

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Breastfeeding is not recommended during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects: Documented in animals

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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

- 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

- INR; more frequently in patients receiving warfarin

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J - Administrative Information

Outpatient prescription for home administration

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K - References

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.

Regorafenib drug monograph, Ontario Health (Cancer Care Ontario).

August 2023 Modified Dosage in hepatic / renal impairment, Dosage in the elderly, Interactions and Pregnancy/lactation sections

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

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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