Regorafenib Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement Status*
Treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy	C18	00244a	CDS
Treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib	C26	00244b	CDS

*This applies to post 2012 indications only

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Regorafenib is taken once daily for 21 days followed by 7 days off therapy.
This 28 day period is considered a treatment cycle.
Treatment is continued until disease progression or unacceptable toxicity develops.

Day	Drug	Dose	Route	Cycle
1-21	Regorafenib	160mg daily	PO	Repeat every 28 days
Regorafenib should be taken at the same time each day,with or without food. The tablets should be swallowed whole with water after a light meal that contains less than 30% fat. An example of a light (low-fat) meal would include 1 portion of cereal (about 30g), 1 glass of skimmed milk, 1 slice of toast with jam, 1 glass of apple juice, and 1 cup of coffee or tea (520 calories, 2g fat).				
If a dose is missed, then it should be taken on the same day as soon as the patient remembers. The patient should not take two doses on the same day to make up for a missed dose. In case of vomiting after regorafenib administration, the patient should not take additional tablets.				
Regorafenib is commonly available as 40mg tablets.				

ELIGIBILITY:

- Indications as above
- ECOG status 0-1
- Adequate bone marrow, renal and liver function

EXCLUSIONS:

- Hypersensitivity to regorafenib or any of the excipients
- Unstable angina or new onset angina (within 3 months), recent MI, cardiac failure
- Severe hepatic impairment
- Pregnancy and lactation

CAUTION:

- In patients with hypersensitivity to any drugs in the same class

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Thyroid function test
- Lipase, amylase as clinically indicated
- Blood pressure
- ECG/QT interval evaluation for patients at risk.

Regular tests:

- FBC, and renal profile
- Liver profile every 2 weeks for first 2 months and then monthly or as clinically indicated
- Thyroid function test, lipase, amylase as clinically indicated
- Close monitoring of INR in patients receiving warfarin
- Blood pressure weekly for first 6 weeks of therapy, then prior to each cycle or as clinically indicated
- ECG and heart rate monitor for cardiotoxicity as required

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Dose interruptions and/or dose reductions may be required based on individual safety and tolerability.
- Dose modifications are to be applied in 40mg (one tablet) steps.
- The lowest recommended daily dose is 80mg.
- The maximum daily dose is 160mg.

Renal and Hepatic Impairment:

Table 1: Dose modification of regorafenib in renal and hepatic impairment

Renal Impairment	Hepatic Impairment	Dose
No dose adjustment is needed. Haemodialysis: No need for dose adjustment is expected	Mild (Child Pugh A)	No dose adjustment is needed
	Moderate (Child Pugh B)	No need for dose adjustment is expected
	Severe (Child Pugh C)	Not recommended

Management of adverse events:

Table 2: Recommended dose modifications of regorafenib and measured for hand-foot skin reaction (HFSR)/palmar-plantar erythrodysesthesia syndrome

Skin Toxicity Grade	Occurrence	Recommended dose modification and measures
Grade 1	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief.
Grade 2	1st occurrence	Decrease dose by 40mg (one tablet) and immediately institute supportive measures. If no improvement occurs despite dose reduction, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1. Dose re-escalation is permitted at the discretion of the physician.
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.
	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.
	4th occurrence	Discontinue treatment permanently.
Grade 3	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40mg (one tablet). A dose re-escalation is permitted at the discretion of the physician.
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When re-starting treatment, decrease dose by 40mg (one tablet).
	3rd occurrence	Discontinue treatment permanently.

Table 3: Recommended measures and dose modifications in case of drug-related liver function test abnormalities

Observed elevations of ALT and/or AST	Occurrence	Recommended measures and dose modification
≤ 5 x ULN (maximum Grade 2)	Any occurrence	Continue regorafenib treatment. Monitor liver function weekly until transaminases return to < 3 x ULN or baseline.
> 5 x ULN ≤ 20 x ULN (Grade 3)	First occurrence	Interrupt treatment with regorafenib. Monitor transaminases weekly until return to < 3 x ULN or baseline. Restart: If the potential benefit outweighs the risk of hepatotoxicity, re-start treatment, reduce dose by 40mg (one tablet), and monitor liver function weekly for at least 4 weeks.
	Re-occurrence	DISCONTINUE treatment with regorafenib permanently.
> 20 x ULN (Grade 4)	Any occurrence	DISCONTINUE treatment with regorafenib permanently.
> 3 x ULN (Grade 2 or higher) with concurrent bilirubin > 2 x ULN	Any occurrence	DISCONTINUE treatment with regorafenib permanently. Monitor liver function weekly until resolution or return to baseline. Exception: patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST.

Table 4: Management of treatment-emergent hypertension.

*Grade of event	Occurrence	Management
Grade 1 Pre Hypertension (systolic BP 120-139mmHg or diastolic BP 80-89mmHg)		Consider increasing the frequency of blood pressure monitoring.
Grade 2 Stage 1 hypertension (systolic BP 140-159mmHg or diastolic BP 90-99mmHg); medical intervention indicated	Asymptomatic Grade 2 (recurrent or persistent (=24hrs) increase by >200mmHg (diastolic) or to > 150/100	Begin anti-hypertensive therapy and continue regorafenib. If diastolic BP is not controlled (≤100 mmHg) with the addition of new therapy, reduce 1 dose level[a].
	Symptomatic Grade 2 (any increase by >20 mmHg (diastolic) or to >150/100, associated with symptoms)	Hold regorafenib until symptoms resolve AND diastolic BP ≤100 mmHg[b]; also treat subject with anti-hypertensive medications. If diastolic BP is not controlled (≤100 mmHg) with the addition of new therapy, reduce 1 dose level[a].
Grade 3 Stage 2 hypertension (systolic BP ≥ 160mmHg or diastolic BP ≥ 100mmHg); medical intervention indicated		Hold regorafenib until symptoms resolve AND diastolic BP ≤100 mmHg[b] and increase current anti- hypertensive medication(s)/add additional anti- hypertensive medications. When regorafenib is restarted, reduce by 1 dose level[a]. If diastolic BP is not controlled (≤100 mmHg) with the addition of more intensive therapy, reduce another dose level [c].
Grade 4 Life threatening consequences urgent intervention indicated		Discontinue therapy.
[a]BP remains controlled for at least one full cycle, dose re-escalation is permitted at the physician's discretion. [b]Subjects requiring a delay of >4 weeks should go off protocol therapy. [c]Subjects requiring >2 dose reductions (<80mg) should go off protocol therapy.		

*CTCAE 4.03

Table 5: Dose modification/delay for toxicities related to regorafenib treatment (except liver function abnormalities, hand-foot skin reaction and hypertension)[a]

Grade of Event	Dose interruption	Dose modification	Dose for subsequent cycles
Grade 0-2	Treat on time	No change	No change
Grade 3	Delay until < Grade 2[b]	Reduce dose by 40mg.	If toxicity remains < Grade 2, dose re-escalation can be considered at the discretion of the treating physician. If dose is re-escalated and toxicity (≥ Grade 3) recurs, institute permanent dose reduction
Grade 4	Delay until < Grade 2 [b]	Reduce dose by 40mg. Permanent discontinuation can be considered at treating consultant's discretion.	
[a] Excludes alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity and asymptomatic laboratory abnormalities. [b] If no recovery after a 4 week delay, treatment will be permanently discontinued.			

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

As outlined in NCCP Classification Document for Systemic Anti Cancer Therapy (SACT) Induced Nausea and Vomiting - Available on the NCCP website

Regorafenib: Minimal to Low (**Refer to local policy).**

Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

See local skin care policy for the prevention and treatment of hand-foot skin adverse reactions

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

1. Grothey A, Van Cutsem E et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. The Lancet.2013;381: 303-312
2. Demetri GD 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;381:295-302.
3. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00216-4/fulltext
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V6 2025. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
5. Regorafenib (Stivarga®) Summary of Product Characteristics.Last updated: 15/10/2019. Accessed Jan 2025. Available at: https://www.ema.europa.eu/en/documents/product-information/stivarga-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	1/10/15	Initial Draft	Dr Greg Leonard/ Dr Maccon Keane
2	25/02/2016	Amendment made to table 1and to footnote at table 4 to clarify dose re-escalation at physician discretion. Amendment made to clarify reimbursement category as High-tech	Dr Maccon Keane
3	22/02/2018	Updated with new NCCP regimen template	Prof Maccon Keane
4	26/02/2020	Reviewed. Update of emetogenic potential and adverse events.	Prof Maccon Keane
5	25/03/2025	Regimen reviewed. Updated eligibility and regular testing section. Updated renal and hepatic dose modifications to align with Giraud et al 2023.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.