Regorafenib Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*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

**If the reimbursement status[1] is not defined, the indication has yet to be assessed through the formal HSE reimbursement process.*

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 With or without food	Repeat every 28 days
Regorafenib should be taken at the same time each day. 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 30 g), 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, 2 g 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 available as 40mg tablets				

ELIGIBILTY:

- Indications as above
- Life expectancy of at least 6 months
- 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

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

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 40 mg (one tablet) steps.
- The lowest recommended daily dose is 80 mg.
- The maximum daily dose is 160 mg.

Renal and Hepatic Impairment:

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

Renal Impairment	Hepatic Impairment
No dose adjustment necessary	Regorafenib is mainly eliminated via the hepatic route. No dose adjustment is required in patients with mild (Child Pugh A) hepatic impairment. There is insufficient data for dose recommendation in moderate hepatic impairment (Child Pugh B). Regorafenib is not recommended in severe hepatic impairment (Child Pugh C

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 40 mg (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 40 mg (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 40 mg (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 40 mg (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 40 mg (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 40 mg (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 (<80 mg) 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: Low (**Refer to local policy).**

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 / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Hepatoxicity:** Abnormalities of liver function tests and bilirubin have been frequently observed in patients treated with regorafenib. Severe liver function test abnormalities (Grade 3 to 4) and hepatic dysfunction with clinical manifestations (including fatal outcomes) have been reported in a small proportion of patients. It is recommended to perform liver function tests (ALT, AST and bilirubin) before initiation of treatment and monitor closely (at least every two weeks) during the first 2 months of treatment. Thereafter, periodic monitoring should be continued at least monthly and as clinically indicated.

  Regorafenib is a uridinediphosphateglucuronosyltransferase (UGT) 1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinaemia may occur in patients with Gilbert's syndrome. For patients with observed worsening of liver function tests considered related to treatment with regorafenib (i.e. where no alternative cause is evident, such as post-hepatic cholestasis or disease progression), the dose modification and monitoring advice in Table 3 should be followed.

  Regorafenib is eliminated mainly via the hepatic route. Close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment.
- **Haemorrhage:** Regorafenib has been associated with an increased incidence of haemorrhagic events, some of which were fatal. Blood counts and coagulation parameters should be monitored in patients with conditions predisposing to bleeding, and in those treated with anticoagulants (e.g. warfarin and phenprocoumon) or other concomitant medicinal products that increase the risk of bleeding. In the event of severe bleeding necessitating urgent medical intervention, permanent discontinuation of regorafenib should be considered.
- **Cardiac ischaemia and infarction:** Regorafenib has been associated with an increased incidence of myocardial ischaemia and infarction Patients with a history of ischaemic heart disease should be monitored for clinical signs and symptoms of myocardial ischaemia. In patients who develop cardiac ischaemia and/or infarction, interruption of regorafenib therapy is recommended until resolution. The decision to re-start therapy should be based on careful consideration of the potential benefits and risks of the individual patient. Regorafenib should be permanently discontinued if there is no resolution.
- **Posterior reversible encephalopathy syndrome (PRES):** PRES has been reported in association with regorafenib treatment A diagnosis of PRES requires confirmation by brain imaging. In patients developing PRES, discontinuation of regorafenib, along with control of hypertension and supportive medical management of other symptoms is recommended.

- **Gastrointestinal perforation and fistula:** Gastrointestinal perforation and fistulae have been reported in patients treated with regorafenib. These events are also known to be common disease-related complications in patients with intra-abdominal malignancies. Discontinuation of regorafenib is recommended in patients developing gastrointestinal perforation or fistula.
- **Arterial hypertension:** Regorafenib has been associated with an increased incidence of arterial hypertension. Blood pressure should be controlled prior to initiation of treatment with regorafenib. It is recommended to monitor blood pressure and to treat hypertension in accordance with standard medical practice. In cases of severe or persistent hypertension despite adequate medical management, treatment should be temporarily interrupted and/or the dose reduced at the discretion of the consultant. In case of hypertensive crisis, treatment should be discontinued.
- **Dermatological toxicity:** Hand-foot skin reaction or palmar-plantar erythrodysesthesia syndrome and rash represent the most frequently observed dermatological adverse reactions with regorafenib.
- Wound healing: Temporary interruption of regorafenib is recommended for precautionary reasons in patients undergoing major surgical procedures. The decision to resume treatment with regorafenib following major surgical intervention should be based on clinical judgment of adequate wound healing.
- **Important information about some of the ingredients**: Each daily dose of 160 mg contains 2.427 mmol (or 55.8 mg) of sodium. To be taken into consideration by patients on a controlled sodium diet. Each daily dose of 160 mg contains 1.68 mg of lecithin (derived from soya).

DRUG INTERACTIONS:

- In vitro data indicate that regorafenib is metabolized by CYP3A4 and uridinediphosphateglucuronsyltransferase UGT1A9.
- Concomitant use of strong inhibitors of CYP3A4 should be avoided as their influence on the steady state exposure of regorafenib has not been studied. Patients should also be counselled with regard to consumption of grapefruit and grapefruit juice.
- Co-administration of a strong UGT1A9 inhibitor (e.g. mefenamic acid, diflunisal, and niflumic acid) during regorafenib treatment should be avoided, as their influence on the steady-state exposure of regorafenib and its metabolites has not been studied.
- Strong inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered.
- In vitro data indicate that regorafenib is an inhibitor of breast cancer resistance protein (BCRP) and p-glycoprotein.
- Co-administration of antibiotics that affect the flora of the gastrointestinal tract may interfere with the enterohepatic circulation of regorafenib and may result in a decreased regorafenib exposure. The clinical significance of these potential interactions is unknown.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Regorafenib - L01XE21

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. Stivarga® Summary of Product Characteristics Accessed Feb 2018 Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002573/WC500149164.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

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/