Regorafenib

Indication
Treatment of metastatic colorectal cancer in patients who have previously received or are not suitable for other available therapies including: fluoropyrimidine based therapy and anti-EGFR based treatment

Treatment of unresectable or metastatic gastrointestinal stromal tumours (GIST) in patients who have progressed on or are intolerant to prior treatment with imatinib and sunitinib. ECOG PS 0-1.

Second line locally advanced or metastatic hepatocellular carcinoma

Regimen details

Day	Drug	Dose	Route
1-21	Regorafenib	160mg once daily	PO

Cycle frequency
28 days (ie. 21 days of treatment followed by 7 days off)

Number of cycles
Continued until progression or unacceptable toxicity

Administration
Regorafenib is available as 40mg capsules
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.
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. If a patient vomits after regorafenib administration, they should be advised NOT to take additional tablets

Pre-medication
Nil

Emetogenicity
This regimen has low emetogenic potential

Additional supportive medication
Topical emollients to prevent PPE

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs (including AST)	14 days
Bone profile	14 days
CEA (colorectal cancer)	14 days
Hepatitis B serology (HBsAG, HBcAb)	none
HbA1c	3 months
Random glucose	14 days
Calculated Creatinine Clearance	14 days
Blood pressure*	Baseline
Coagulation screen	If pre-disposition to bleeding or on anticoagulants
ECG	If cardiac history

- **Blood pressure should be controlled prior to commencing treatment**

Investigations - pre subsequent cycles

FBC, U&Es, LFT (including AST), calculated creatinine clearance, calcium, magnesium, random glucose, CEA (colorectal cancer) and blood pressure every 4 weeks.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	Limit
Neutrophils	≥ 1.5 x 10^9/L
Platelets	≥ 75 x 10^9/L
Bilirubin	< 2 x ULN
AST/ALT	<3 x ULN
Creatinine Clearance (CrCl)	≥ 30 mL/min

Dose modifications

Dose interruptions and/or dose reductions may be required. Dose reductions should be in 40 mg (one tablet) steps. The lowest recommended daily dose is 80 mg. The maximum daily dose is 160 mg.

- **Haematological toxicity**

Treatment should be withheld and recommenced as per the table below:
Regorafenib has been associated with an increased incidence of haemorrhagic events, some of which have been fatal. Blood counts and coagulation parameters should be monitored in patients with conditions predisposing to bleeding, and in those treated with anticoagulants or other concomitant medicinal products that increase the risk of bleeding. In the event of severe bleeding requiring urgent medical intervention, regorafenib should be permanently discontinued. Discuss with consultant if neutrophils <1.0 x10^9/L

- **Renal impairment**

No dose modifications required for renal impairment. Regorafenib has not been studied in patients with severe renal impairment or end-stage renal disease..

- **Hepatic impairment**

Regorafenib is mainly eliminated via the hepatic route. No dose adjustments are recommended in patients with mild hepatic impairment. There is only limited data for use in moderate hepatic impairment so caution and close monitoring is required. Regorafenib is not recommended in severe hepatic impairment.

Abnormalities of liver function tests (AST/ALT and bilirubin) have been frequently observed. 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. If worsening LFTs are observed the following is recommended:

AST/ALT (x ULN)		**Action**
≤ 5 x ULN		Continue treatment. Monitor LFTs weekly until AST/ALT < 3 x ULN or baseline.
5 - ≤ 20 x ULN	1st occurrence	Withhold treatment. Monitor LFTs weekly until AST/ALT < 3 x ULN or baseline. If benefit outweighs risk restart with 40mg dose reduction and monitor LFTs weekly for at least 4 weeks.
	Further occurrence	Discontinue treatment.
> 20 x ULN		Discontinue treatment.
> 3 x ULN **and** bilirubin > 2 x ULN*		Discontinue treatment. Monitor LFTs weekly until resolution or baseline.

* Exception is patients with Gilberts syndrome: treat as per recommendations above for AST/ALT elevations.

- **Other toxicities**

Gastrointestinal perforation and fistula: Regorafenib should be discontinued.

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. Screening for and subsequent treatment of oesophageal varices in patients with liver cirrhosis should be performed as per standard of care before starting treatment with regorafenib. In the event of severe bleeding necessitating urgent medical intervention, permanent discontinuation of regorafenib should be considered.

Hypertension: Blood pressure must be controlled prior to commencing treatment and should be regularly monitored during treatment.

The use of vascular endothelial growth factor (VEGF) pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating regorafenib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Regorafenib has been associated with an increased incidence of arterial hypertension. Blood pressure should be controlled prior to initiation of treatment. 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 physician. In case of hypertensive crisis, regorafenib should be discontinued.

Cardiac ischaemia: 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, regorafenib should be withheld until resolution. The decision to re-start regorafenib therapy should be based on careful consideration of the potential benefits and risks for the individual patient. Regorafenib should be permanently discontinued if there is no resolution.

Wound healing complications: Regorafenib may suppress or interfere with wound healing. Treatment should be withheld for precautionary reasons in patients undergoing major surgical procedures. The decision to resume treatment following major surgical intervention should be based on clinical assessment of adequate wound healing.

Thrombotic microangiopathy (TMA): Thrombotic microangiopathy (TMA), including thrombotic thrombocytopaenic purpura (TTP), have been associated with the use of regorafenib. The diagnosis of TMA should be considered in patients presenting with haemolytic anaemia, thrombocytopenia, fatigue, fluctuating neurological manifestation, renal impairment, and fever. Regorafenib therapy should be discontinued in patients who develop TMA and prompt treatment is required. Reversal of the effects of TMA has been observed after treatment discontinuation.

Skin toxicity:

Toxicity Grade		**Action**
Grade 1		Continue treatment. Commence supportive symptomatic treatment
Grade 2	1st occurrence	Continue with 40mg dose reduction. Commence supportive symptomatic treatment. If no improvement within 7 days, withhold until ≤ Grade 1. (Dose may be escalated after discussion with consultant)
	2nd occurrence	Withhold until ≤ Grade 1. Recommence with 40mg dose reduction. (Dose may be escalated after discussion with consultant)
	3rd occurrence	Withhold until ≤ Grade 1. Recommence with 40mg dose reduction. (Dose may be escalated after discussion with consultant)
	4th occurrence	Discontinue treatment.
Grade 3	1st occurrence	Commence supportive symptomatic treatment. Withhold treatment for minimum of 7 days until ≤ Grade 1. Recommence with 40mg dose reduction. (Dose may be escalated after discussion with consultant)
	2nd occurrence	Commence supportive symptomatic treatment. Withhold treatment for minimum of 7 days until ≤ Grade 1. Recommence with 40mg dose reduction.
	3rd occurrence	Discontinue treatment.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Haemorrhage
Gastrointestinal perforation and fistula
Myocardial infarction and ischaemia
Aortic dissection
Posterior reversible encephalopathy syndrome (PRES)

Arterial hypertension
Neutropenia Infections
Wound healing complications
Altered LFTs

- **Frequently occurring side effects**

Palmar-plantar erythrodysesthesia (PPE)
Electrolyte abnormalities (hypophosphataemia, hypocalcaemia, hyponatraemia, hypokalaemia)
Metabolic abnormalities
Fatigue
Taste disturbance

- **Other side effects**

Reduced appetite
Increased INR (caution for patients on warfarin)

Significant drug interactions – for full details consult product literature/ reference texts

Regorafenib is metabolized by cytochrome CYP3A4
Strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, grapefruit juice, itraconazole, posaconazole, teithromycin, voriconazole): avoid concomitant use, may increase exposure to regorafenib.
Strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, St John's Wort): avoid concomitant use, may reduce exposure to regorafenib.
Strong UGT1A9 inhibitors (e.g. mefenamic acid, diflunisal, and niflumic acid): avoid concomitant use, effect on exposure of regorafenib and its metabolites has not been studied.
UGT1A1 and UGT1A9 substrates: co-administration of regorafenib may increase systemic exposure to UGT1A1 and UGT1A9 substrates.
BCRP substrates (e.g. methotrexate, fluvastatin, rosuvastatin, atorvastatin): monitor patients closely for signs and symptoms of increased exposure to BCRP substrates.
Bile salt-sequestering agents (e.g. cholestyramine and cholestagel): may interact with regorafenib by forming insoluble complexes, resulting in potentially decreased exposure. The clinical significance is unknown.

Additional comments

Nil

Fertility/Contraception

Patients should use an acceptable method of birth control to avoid pregnancy for the duration of treatment and for 6 months afterwards. Breastfeeding should be discontinued during treatment. Women using hormonal contraceptive must also use a barrier contraceptive method.

References

- Colorectal NICE guideline NG151 (updated 15 Dec 2021) accessed 16 June 2025
- Summary of Product Characteristics Regorafenib accessed 16 June 2025 available at http://www.medicines.org.uk
- Demetri, G.D, 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. The Lancet 2013. 281: 9863. p295-302
- Regorafenib for previously treated metastatic colorectal cancer. Technology appraisal guidance TA866 8th Feb 2023 accessed 16th June 2025 available at https://www.nice.org.uk/guidance/ta866

THIS PROTOCOL HAS BEEN DIRECTED BY DR WILLIAMSON DESIGNATED LEAD CLINICIAN FOR COLORECTAL CANCER
RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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