Regorafenib

Indication
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.

(NICE TA488)

ICD-10 codes
Codes with a pre fix C49

Regimen details

Day	Drug	Dose	Route
1-21	Regorafenib	160mg OD	PO

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

Number of cycles
Continued until disease progression or unacceptable toxicity.

Administration
Regorafenib is available as 40mg capsules.

Patients should be advised to take the tablets at the same time each day. Tablets should be swallowed whole with a glass of water after a light, low fat (less than 30% fat) meal. 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 emetic potential.

Additional supportive medication
Keratolytic creams and moisturising creams should be used for prevention and symptomatic relief of palmar plantar erythema (PPE).

Extravasation
N/A

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+Es (including creatinine)	14 days
LFTs	14 days
Calcium	14 days
Phosphate	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

Investigation	Validity period
FBC	Every 4 weeks
U+Es (including creatinine)	Every 4 weeks
LFTs	Every 2 weeks for the first 2 months, then every 4 weeks.
Calcium	Every 4 weeks
Blood pressure	As clinically indicated

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	≥ 1.0 x 10^9/L
Platelets	> 100 x 10^9/L
Creatinine clearance	> 30 mL/min
AST/ALT	< 3 x ULN
Bilirubin	< 2 x ULN

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**

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 x 10^9/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**

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.

Gastrointestinal perforation and fistula:
Regorafenib should be discontinued.

Haemorrhage (see above)

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

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.

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

- **Serious side effects**

Haemorrhage
Gastrointestinal perforation and fistula
Myocardial infarction and ischaemia
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

- **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.

Anticoagulants: increased risk of bleeding.

Additional comments

Nil

References

- Summary of Product Characteristics – Regorafenib (Bayer) accessed 22 March 2018 via www.medicines.org.uk
- National Institute for Health and Clinical Excellence. NICE Technology Appraisal Guidance 488 accessed 22 March 2018 via www.nice.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

Written/reviewed by: Dr S Falk (Consultant Oncologist, UHBristol NHS Trust)

Checked by: Sarah Murdoch (Senior Oncology/Haematology Pharmacist, SW Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Clinical Network)

Date: May 2018