EVEROLIMUS

Blueteq registration is required before treatment may start.

1. Licensed for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

2. Licensed for the treatment of ER +ve, HER2 -ve advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor.

3. The treatment of unresectable or metastatic neuroendocrine tumours of pancreatic, gastro-intestinal or lung origin, with disease progression

Drug/Dosage: **Everolimus** initiate at 10mg po once daily continuous therapy

Other Drugs: *For **breast cancer** patients, to be prescribed in combination with:*
Exemestane 25mg po once daily continuous therapy

Administration: Everolimus is available as 2.5mg, 5mg and 10mg tablets, which may be taken at the same time of day every day either with or without food, but not after a high fat meal. Grapefruit and grapefruit juice should be avoided while on everolimus.

Frequency: Clinical review every 4 weeks.
Continue until disease progression or unacceptable adverse events.

Main Toxicities: mucositis; rash or dry skin or PPE; fatigue; diarrhoea; oedema; myelosuppression; increased risk of infection; change in sense of taste; non-infectious pneumonitis (can be severe – any shortness of breath should be reported); hyperglycaemia; hypertriglyceridaemia; headache

Anti- emetics: mildly emetogenic (anti-emetics not routinely needed)

Regular:	FBC	every 4 weeks
Investigations:	LFTs	every 4 weeks
	U&Es	every 4 weeks
	Random blood glucose*	baseline, then: for non-diabetics: before the 2nd and 3rd month's supply is dispensed as a minimum for patients with a history of diabetes, or previous raised blood glucose: continue to monitor every month
	*Fasting glucose	only if random blood glucose > 11 mmol/l
	Triglycerides	baseline, then periodically, according to Consultant preference

Comments: Elimination of everolimus is mainly through hepatic metabolism. Concomitant use of enzyme inducers (e.g. carbamazepine, phenytoin, St Johns wort) with everolimus should be avoided, as this may increase the risk of therapeutic failure. Continuing with the enzyme inducer while increasing the everolimus dose above 10mg daily is not an option however, as there is no clinical evidence of benefit and so no funding for this.

Co-administration of everolimus with potent CYP3A4 enzyme inhibitors (eg itraconazole, clarithromycin) or grapefruit juice is not recommended.

Reason for Update: neuroendocrine indications added	Approved by Consultant: Dr A Michael
Version: 4	Approved by Lead Chemotherapy Nurse: S Wills-Percy
Supersedes: Version 3	Date: 8.6.17
Prepared by: S Taylor	Checked by: C Tucker

Co-administration with moderate enzyme inhibitors (eg erythromycin, fluconazole, verapamil) should be avoided. If this is not possible, the dose of everolimus may need to be reduced to 5mg daily or 2.5mg daily according to tolerability.

Dose Modifications

Haematological Toxicity:	Neutrophils 0.5 – 0.99 x 10^9/l or Platelets 50 - 74 x 10^9/l	Interrupt treatment until neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 75 x 10^9/L, then re-start at the same dose.
	Neutrophils < 0.5 x 10^9/l or Platelets < 50 x 10^9/l	Interrupt treatment until neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 75 x 10^9/L, then re-start at the 5mg dose.
	Grade 3 febrile neutropenia (neutrophils 0.5 - 0.9 x 10^9/l)	Interrupt treatment until fever resolved and neutrophils ≥ 1.25 x 10^9/L, then re-start at 5mg dose.
	Grade 4 febrile neutropenia (neutrophils < 0.5 x 10^9/l)	Discontinue everolimus permanently.

Hyperglycaemia or Dyslipidaemia: If blood glucose is raised at baseline, whenever possible, optimal glycaemic control should be achieved before starting everolimus.

Once everolimus has started, follow the advice below:

Fasting glucose 14 - 27.8 mmol/l or Triglycerides 5.8 - 11.4 mmol/l	Interrupt everolimus until resolved. Re-initiate everolimus at 5mg daily.
Fasting glucose > 27.8 mmol/l or Triglycerides > 11.4 mmol/l	Discontinue everolimus permanently.

Mucositis: Symptoms should be managed according to the Alliance guidelines for prevention and management of mucositis.

Grading of Mucositis	Management
Grade 2, first episode	Everolimus may continue if the patient can tolerate it. Otherwise, interrupt until ≤ Grade 1, then try and re-introduce at the same dose.
Grade 2, second episode	Interrupt treatment until ≤ Grade 1, then re-start everolimus at 5mg daily.
Grade 3	Everolimus treatment should be interrupted until ≤ Grade 1. Then re-start everolimus at 5mg once daily. If Grade 3 toxicity recurs, consider stopping permanently
Grade 4	Discontinue everolimus permanently.

Non-infectious Pneumonitis: Patients who develop radiological changes suggestive of non-infectious pneumonitis should be managed as follows:

Grading of Pneumonitis	Management
Grade 2 (symptomatic, not affecting ADL)	Consider interrupting therapy until symptoms resolve, then re-initiate everolimus at 5mg daily. Discontinue if symptoms do not resolve within 4 weeks.
Grade 3 (symptomatic, affecting ADL, requiring O_2)	Interrupt therapy until symptoms resolve. The use of corticosteroids may be indicated until symptoms resolve. Consider re-initiating everolimus at 5mg daily.
Grade 4 (life-threatening)	Discontinue everolimus. Corticosteroids may be required until symptoms resolve.

Any Other Toxicities:

Other Non-Haematological Toxicity	Management
Grade 2	If toxicity is tolerable, no dose adjustment required. If toxicity becomes intolerable, interrupt everolimus until recovery to Grade ≤1. Re-initiate treatment at same dose. If toxicity recurs at Grade 2, interrupt treatment until recovery to Grade ≤1. Re-initiate treatment at 5 mg daily.
Grade 3	Interrupt everolimus until recovery to Grade ≤1. Consider re-initiating treatment at 5 mg daily. If toxicity recurs at Grade 3, consider discontinuation.
Grade 4	Discontinue everolimus permanently

Hepatic Impairment:

Degree of hepatic impairment	Recommended Everolimus Dose
Mild (Child-Pugh A)	7.5mg daily
Moderate (Child-Pugh B)	5mg daily
Severe (Child-Pugh C)	use only if desired benefit outweighs risk, and do not exceed a dose of 2.5mg daily

Renal Impairment: No dose adjustment is required.

References:

Motzer et al; Lancet 2008; 372 (9637): 449 – 456 (rcc)
Baselga, J et al; NEJM 2012; 366: 520 – 529 (breast)
Yao, J et al; NEJM 2011; 364: 514 – 523
Yao, J et al; Lancet 2015; 387 (10022): 968 - 977