Everolimus for Neuroendocrine Tumours

Indication	The treatment of unresectable or metastatic neuroendocrine tumours of pancreatic, gastrointestinal or lung origin with disease progression.
Treatment Intent	Palliative
Frequency and number of cycles	Repeated every 28 days (30 days treatment should be dispensed) Continue until progression of disease or unacceptable toxicity or patient choice.
Monitoring parameters	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • **Hyperglycaemia** has been reported. Monitoring of fasting serum glucose is recommended prior to the start of Everolimus therapy and every 3 months thereafter. More frequent monitoring is recommended when Everolimus is co-administered with other medicinal products that may induce hyperglycaemia. When possible, optimal glycaemic control should be achieved before starting a patient on Everolimus. • **Dyslipidaemia** (including hypercholesterolaemia and hypertriglyceridaemia) has been reported. Monitoring of blood cholesterol and triglycerides prior to the start of Everolimus therapy and every 3 months thereafter, as well as management with appropriate medical therapy, is recommended. • Monitor FBC, LFT's and U&E's prior to each cycle. • If neuts 1.0-1.4 and/or platelets 75-100 d/w consultant, if neuts <1.0 or platelets <75 defer 1 week. • **Hepatic Impairment:** A dose reduction to 7.5mg OD is recommended in mild hepatic impairment (Child-Pugh A). A dose reduction to 5mg once daily is recommended in moderate hepatic impairment (Child-Pugh B), and a reduction to 2.5mg OD is recommended in severe hepatic impairment (Child-Pugh C) where benefit outweighs risk. • **Renal Impairment:** No dose reduction required in renal impairment. • **Dose modification:** If a dose modification is required the dose may be reduced or temporarily withheld followed by a reintroduction at 5mg daily, see table 1 below. • For adverse reactions of Grade 1, dose adjustment is usually not required. If dose reduction is required, the recommended dose is 5 mg daily and must not be lower than 5 mg daily. Commence appropriate supportive measures before instituting dose reductions. • **Stomatitis,** including mouth ulcerations and oral mucositis, can occur very commonly during treatment usually within the first 8 weeks of treatment. Patients should be counselled to seek medical attention should symptoms occur and be provided supportive care when required. See KMCC website SACT induced mucositis & stomatitis: http://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/sact-pathways-guidelines-for-the-management-of-sact-induced-adverse-reactions-and-nursing/ • **Non-infectious pneumonitis** is a class effect; patients should be advised to report promptly any new or worsening respiratory symptoms • **Infections:** Everolimus has immunosuppressive properties and may pre-dispose patients to bacterial, fungal, viral and protozoan infections including reactivation of hepatitis B. Ensure patients are monitored appropriately. Cases of PJP/PCP, some with fatal outcome, have

	been reported in patients who received everolimus. PJP/PCP may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP/PCP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required. • **Impaired wound healing:** Caution should therefore be exercised with the use of everolimus in the peri-surgical period. • **Drug Interactions (for comprehensive list refer to BNF/SPC):** o Co-administration with inhibitors (e.g. ketoconazole, itraconazole, clarithromycin) and inducers (e.g rifampicin, dexamethasone, phenytoin, and carbamazepine) of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a ***moderate*** CYP3A4 and/or PgP inhibitor or inducer cannot be avoided monitor closely and dose adjustments of everolimus can be taken into consideration based on predicted AUC (see table 2 in SPC). o Preparations containing St John's Wort should not be used during treatment with everolimus. o Concomitant treatment with ***potent*** CYP3A4 and P-gp inhibitors (e.g ketoconazole, itraconazole, clarithromycin) result in dramatically increased plasma concentrations of everolimus. There are currently not sufficient data to allow dosing recommendations in this situation and concomitant treatment of everolimus and ***potent*** inhibitors is not recommended. Caution should be exercised when everolimus is taken in combination with orally administered CYP3A4 substrates with a narrow therapeutic index (e.g. pimozide, terfenadine, astemizole, cisapride, quinidine or ergot alkaloid derivatives), and the patient should be monitored for undesirable effects. o Patients taking concomitant ACE inhibitor (e.g. ramipril) therapy may be at increased risk for angioedema. o Use of live vaccines should be avoided during treatment with everolimus. • **Missed dose:** If a patient misses a dose it should be omitted and then resume with the next scheduled dose, additional tablets should not be taken. • **Driving and machinery:** Everolimus can potentially cause fatigue in some patients and therefore should be advised to be cautious when driving or using machines. • **For oral self-administration:** refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet.
Reference(s)	KMCC protocol UGI-040 V4 SPC assessed online 11.07.2025

NB for funding information, refer to CDF and NICE Drugs Funding List

Table 1: Management of Adverse Reactions

Adverse reaction	Severity[1]	Everolimus dose adjustment
Non-infectious pneumonitis	Grade 2	Consider interruption of therapy until symptoms improve to Grade ≤1. Re-initiate treatment at 5 mg daily. Discontinue treatment if failure to recover within 4 weeks.
	Grade 3	Interrupt treatment until symptoms resolve to Grade ≤1. Consider re-initiating treatment at 5 mg daily. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue treatment.
Stomatitis	Grade 2	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤1. Re-initiate treatment at 5 mg daily.
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at 5 mg daily.
	Grade 4	Discontinue treatment.
Other non-haematological toxicities (excluding metabolic events)	Grade 2	If toxicity is tolerable, no dose adjustment required. If toxicity becomes intolerable, temporary dose interruption 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	Temporary dose interruption until recovery to Grade ≤1. Consider re-initiating treatment at 5 mg daily. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue treatment.
Metabolic events (e.g. hyperglycaemia, dyslipidaemia)	Grade 2	No dose adjustment required.
	Grade 3	Temporary dose interruption. Re-initiate treatment at 5 mg daily.
	Grade 4	Discontinue treatment.
Thrombocytopenia	Grade 2 (<75, ≥50x10^9/l)	Temporary dose interruption until recovery to Grade ≤1 (≥75x10^9/l). Re-initiate treatment at same dose.
	Grade 3 & 4 (<50x10^9/l)	Temporary dose interruption until recovery to Grade ≤1 (≥75x10^9/l). Re-initiate treatment at 5 mg daily.
Neutropenia	Grade 2 (≥1x10^9/l)	No dose adjustment required.
	Grade 3 (<1, ≥0.5x10^9/l)	Temporary dose interruption until recovery to Grade ≤2 (≥1x10^9/l). Re-initiate treatment at same dose.
	Grade 4 (<0.5x10^9/l)	Temporary dose interruption until recovery to Grade ≤2 (≥1x10^9/l). Re-initiate treatment at 5 mg daily.
Febrile neutropenia	Grade 3	Temporary dose interruption until recovery to Grade ≤2 (≥1.25x10^9/l) and no fever. Re-initiate treatment at 5 mg daily.
	Grade 4	Discontinue treatment.
[1] Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0		

Repeat every 28 days.

TTO	Drug	Dose	Route	Directions
Day 1	**EVEROLIMUS**	**10mg**	PO	Once daily, swallowed whole with a glass of water. Available as 2.5mg, 5mg and 10mg tablets.
	Metoclopramide	10mg	PO	tds when required (dispense 28 tablets on cycle 1, then only if specified)
	Loperamide	2mg-4mg	PO	Take two initially then one after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if required.