# Everolimus (Afinitor®) for Neuroendocrine Tumours

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| **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** | Continue until progression of disease or unacceptable toxicity<br>Repeated every 28 days (30 days treatment should be dispensed) |
| **Monitoring parameters pre-treatment** | • Monitor FBC, LFT's and U&E's prior to each cycle<br>• 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.<br>• 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.<br>• If neuts 1.0-1.4 and/or platelets 75-100 d/w consultant, if neuts <1.0 or platelets <75 defer 1 week. 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.<br>• A dose reduction to 5mg and 10mg on alternate days 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 5mg on alternate days is recommended in severe hepatic impairment where benefit outweighs risk.(Child-Pugh C)<br>• No dose reduction required in renal impairment<br>• Use of live vaccines should be avoided during treatment with everolimus<br>• Non-infectious pneumonitis is a class effect; patients should be advised to report promptly any new or worsening respiratory symptoms<br>• 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<br>• 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, dose adjustments of everolimus can be taken into consideration based on predicted AUC. Concomitant treatment with ***potent*** CYP3A4 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. Patients taking concomitant ACE inhibitor (e.g. ramipril) therapy may be at increased risk for angioedema.<br>• For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet. |

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**Table 1: Management of Adverse Reactions**

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.

| Adverse reaction | Severity[1] | Everolimus dose adjustment |
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| Non-infectious pneumonitis | Grade 2 | Consider interruption of therapy until symptoms improve to Grade ≤1.<br>Re-initiate treatment at 5 mg daily.<br>Discontinue treatment if failure to recover within 4 weeks. |
| | Grade 3 | Interrupt treatment until symptoms resolve to Grade ≤1.<br>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.<br>Re-initiate treatment at same dose.<br>If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤1.<br>Re-initiate treatment at 5 mg daily. |
| | Grade 3 | Temporary dose interruption until recovery to Grade ≤1.<br>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.<br>If toxicity becomes intolerable, temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at same dose.<br>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.<br>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.<br>Re-initiate treatment at 5 mg daily. |
| | Grade 4 | Discontinue treatment. |
| Thrombocytopenia | Grade 2 ($<75, \geq 50 \times 10^9$/l) | Temporary dose interruption until recovery to Grade ≤1 ($\geq 75 \times 10^9$/l). Re-initiate treatment at same dose. |
| | Grade 3 & 4 ($<50 \times 10^9$/l) | Temporary dose interruption until recovery to Grade ≤1 ($\geq 75 \times 10^9$/l). Re-initiate treatment at 5 mg daily. |
| Neutropenia | Grade 2 ($\geq 1 \times 10^9$/l) | No dose adjustment required. |
| | Grade 3 ($<1, \geq 0.5 \times 10^9$/l) | Temporary dose interruption until recovery to Grade ≤2 ($\geq 1 \times 10^9$/l). Re-initiate treatment at same dose. |
| | Grade 4 ($<0.5 \times 10^9$/l) | Temporary dose interruption until recovery to Grade ≤2 ($\geq 1 \times 10^9$/l). Re-initiate treatment at 5 mg daily. |
| Febrile neutropenia | Grade 3 | Temporary dose interruption until recovery to Grade ≤2 ($\geq 1.25 \times 10^9$/l) and no fever.<br>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

**Reference(s)**

NB For funding information, refer to the SACT funding spreadsheet

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| TTO | Drug | Dose | Route | Directions |
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| | **Everolimus** | 10mg | po | Once daily, swallowed whole with a glass of water.<br>(If a dose reduction is required the suggested dose is 5mg daily)<br>Available as 5mg and 10mg tablets. |
| | Metoclopramide | 10mg | po | tds when required (dispense 28 tablets on cycle 1, then only if specified) |
| | Loperamide | 2mg | po | Take two initially then one after each loose stool when required (max.8(16mg) a day) (dispense one original pack on cycle 1 then only if specified) |

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