Everolimus Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.	C64	00320a	CDS
Treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.	C25	00320b	CDS
The treatment of unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumours of gastrointestinal origin in adults with progressive disease	C25	00320c	CDS

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Drug	Dose	Route	Cycle
Everolimus	10mg daily	PO once daily at the same time every day, consistently either with or without food Swallow whole with a glass of water	Continuous
If a dose is missed, the patient should not take an additional dose, but take the next prescribed dose as usual.			
The tablets should **not** be chewed or crushed			

ELIGIBILITY:

- Indication as above
- ECOG performance status 0-2

EXCLUSIONS:

- Hypersensitivity to everolimus, to other rapamycin derivatives or any of the excipients
- Caution is advised for patients with pre-existing significant lung compromise due to the risk for pneumonitis
- Pregnancy
- Lactation

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist,

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Blood urea nitrogen (BUN), urinary protein.
- Total cholesterol and triglycerides
- Fasting serum glucose
- Virology screen -Hepatitis B (HBsAg, HBcoreAb) & C, HIV

*See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

Regular tests:

- FBC, renal and liver profile every 4 weeks
- Total cholesterol and triglycerides
- Monitoring of fasting serum glucose as clinically indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Management of severe and/or intolerable suspected adverse reactions may require dose reduction and/or temporary interruption of everolimus therapy.
- For adverse reactions of Grade 1, dose adjustment is usually not required

Haematological:

Table 1: Dose modification of everolimus in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose recommendation
≥1		≥ 75	No dose adjustment required
0.5-0.99	and/or	50-74.9	Temporary dose interruption until neutrophils recover to ≥1 x 10^9/L and/or platelets recover to ≥75x10^9/l. Re-initiate treatment at same dose.
<0.5	and/or	<50	Temporary dose interruption until neutrophils recover to ≥1 x 10^9/L and/or platelets recover to ≥75x10^9/l. Re-initiate treatment at 5mg daily
Grade 3 Febrile Neutropenia			Temporary dose interruption until recovery to Grade 2 (≥1.25x10^9/L) and no fever. Re-initiate treatment at 5 mg daily.
Grade 4 Febrile Neutropenia			Discontinue treatment

Table 2: Dose modification of everolimus in renal and hepatic impairment

Renal Impairment	Hepatic Impairment*	
No dose adjustment required	Mild (Child Pugh Class A)	7.5mg daily
	Moderate (Child Pugh Class B)	5mg daily
	Severe (Child Pugh Class C)	Only recommended if the desired benefit outweighs the risk. In this case, a dose of 2.5 mg daily must not be exceeded

*Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment

Management of adverse events:

Table 3: Dose Modification of everolimus for Adverse Events

Adverse reactions	Recommended dose modification
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 5mg daily. If toxicity recurs at Grade 3, consider discontinuation.
• Grade 4	Discontinue treatment
Stomatitis	
• Grade 2	
○ 1st occurrence	Temporary dose interruption until recovery to Grade ≤ 1. Re-initiate treatment at same dose.
○ 2nd occurrence	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	
○ 1st occurrence	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.
○ 2nd occurrence	If toxicity recurs at Grade 2, interrupt treatment until recovery to Grade ≤1. Re-initiate treatment at 5 mg daily.
• Grade 3	
○ 1st occurrence	Temporary dose interruption until recovery to Grade ≤1. Consider re-initiating treatment at 5 mg daily.
○ 2nd occurrence	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

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal to Low (**Refer to local policy).**

PREMEDICATIONS: None required

OTHER SUPPORTIVE CARE:

- The use of non-alcoholic prophylactic or therapeutic mouthwashes may be required for the prevention or management of mucositis **(Refer to local policy)**.
- Everolimus may have a minor or moderate influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines if they experience fatigue during treatment with everolimus.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Non-infectious pneumonitis:** This is a class effect of rapamycin derivatives, including everolimus. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnoea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Opportunistic infections such as pneumocystis jirovecii (carinii) pneumonia (PJP, PCP) should be ruled out in the differential diagnosis of non-infectious pneumonitis. Patients should be advised to report promptly any new or worsening respiratory symptoms.
    - Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue everolimus therapy without dose adjustments.
    - If symptoms are moderate (Grade 2) or severe (Grade 3) the use of corticosteroids may be indicated until clinical symptoms resolve.
    - For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for pneumocystis jirovecii (carinii) pneumonia (PJP, PCP) may be considered.
- **Infections:** Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens. Physicians and patients should be aware of the increased risk of infection with everolimus. Pre-existing infections should be treated appropriately and should have resolved fully before starting treatment with everolimus. While taking everolimus, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of everolimus.
- **Hypersensitivity reactions:** Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnoea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus.
- **Oral mucositis:** This is a common side effect with this treatment and may manifest as mouth and tongue ulceration. Early intervention may help to avoid dose alteration or interruption. Topical treatments (alcohol free) are recommended.
- **Wound healing complications:** Impaired wound healing is a class effect of rapamycin derivatives, including everolimus. Caution should therefore be exercised with the use of everolimus in the peri-surgical period.
- **Renal failure events:** Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with everolimus. Renal function should be monitored particularly where patients have additional risk factors that may further impair renal function.

- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy. **(Refer to local infectious disease policy).** These patients should be considered for assessment by hepatology.

DRUG INTERACTIONS:

- Everolimus is a substrate of CYP3A4 enzyme and a substrate and moderate inhibitor of the efflux transport protein P-glycoprotein. Absorption and subsequent elimination of everolimus may be influenced by agents affecting CYP3A4 and/or P-glycoprotein.
  - Co-administration with inhibitors and inducers 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 result in dramatically increased plasma concentrations of everolimus. There are currently not sufficient data to allow dosing recommendations in this situation. Hence, 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 due to the potential for drug interactions. If everolimus is taken with orally administered CYP3A4 substrates with a narrow therapeutic index. The patient should be monitored for undesirable effects described in the product information of the orally administered CYP3A4 substrate.
- Patients taking concomitant ACE inhibitor (e.g. ramipril) therapy may be at increased risk for angioedema.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008;372:449-56.
2. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors.Cancer 2010;116(18):4256-4265.
3. Yao, J et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011;364;6:514-23.
4. Yao, J et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet, The, 2016-03-05, Volume 387, Issue 10022, Pages 968-977
5. Afatinor® Summary of Product Characteristics. Accessed January 2021. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001038/WC500022814.pdf

6. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V2 2019. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	3/5/2016		Prof Maccon Keane
2	3/5/2018	Applied new NCCP regimen template and updated dosing for adverse events as per SmPC	Prof Maccon Keane
3	14/01/2019	Added in new indication 00320c Added in virology screening	Prof Maccon Keane
4	22/01/2021	Updated hepatitis B reactivation standard wording	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.