Everolimus Monotherapy

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>*Reimbursement Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.</td>
<td>C64</td>
<td>00320a</td>
<td>CDS</td>
</tr>
<tr>
<td>Treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.</td>
<td>C7A</td>
<td>00320b</td>
<td>CDS</td>
</tr>
</tbody>
</table>

*If the reimbursement status is not defined*, the indication has yet to be assessed through the formal HSE reimbursement process.

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 patient's individual clinical circumstances.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus</td>
<td>10mg</td>
<td>PO once daily at the same time every day, consistently either with or without food</td>
<td>Continuous</td>
</tr>
<tr>
<td></td>
<td>daily</td>
<td>Swallow whole with a glass of water</td>
<td></td>
</tr>
</tbody>
</table>

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
### 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>
<thead>
<tr>
<th>ANC (x10⁹ /L)</th>
<th>Platelets (x10⁹ /L)</th>
<th>Dose recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1</td>
<td>≥ 75</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td>0.5-0.99 and/or 50-74.9</td>
<td></td>
<td>Temporary dose interruption until neutrophils recover to ≥1 x 10⁹/L and/or platelets recover to ≥75x10⁹/L. Re-initiate treatment at same dose.</td>
</tr>
<tr>
<td>&lt;0.5 and/or &lt;50</td>
<td></td>
<td>Temporary dose interruption until neutrophils recover to ≥1 x 10⁹/L and/or platelets recover to ≥75x10⁹/L. <strong>Re-initiate treatment at 5mg daily</strong></td>
</tr>
</tbody>
</table>

Grade 3 Febrile Neutropenia
Temporary dose interruption until recovery to Grade 2 (≥1.25x10⁹/L) and no fever. Re-initiate treatment at 5 mg daily.

Grade 4 Febrile Neutropenia
Discontinue treatment

#### Renal Impairment

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

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

### Management of adverse events:

<table>
<thead>
<tr>
<th>NCCP Regimen: Everolimus Monotherapy</th>
<th>Published: 03/05/2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour Group: Genitourinary/Neuroendocrine</td>
<td>ISMO Contributor: Prof Maccon Keane</td>
</tr>
<tr>
<td>NCCP Regimen Code: 00320</td>
<td>Version number: 2</td>
</tr>
</tbody>
</table>

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient’s care or treatment. Use of these documents is the responsibility of the prescribing clinician. and is subject to HSE’s terms of use available at [http://www.hse.ie/eng/Disclaimer](http://www.hse.ie/eng/Disclaimer)

This information is valid only on the day of printing, for any updates please check [www.hse.ie/NCCPchemoregimens](http://www.hse.ie/NCCPchemoregimens)
Table 3: Dose Modification of everolimus for Adverse Events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-infectious pneumonitis</td>
<td>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.</td>
</tr>
<tr>
<td>• Grade 2</td>
<td></td>
</tr>
<tr>
<td>• Grade 3</td>
<td>Interrupt treatment until symptoms resolve to Grade ≤ 1. Consider re-initiating treatment at 5mg daily. If toxicity recurs at Grade 3 consider discontinuation.</td>
</tr>
<tr>
<td>• Grade 4</td>
<td>Discontinue treatment</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>Temporary dose interruption until recovery to Grade ≤ 1. Re-initiate treatment at same dose.</td>
</tr>
<tr>
<td>• Grade 2</td>
<td>Note: 1st occurrence:</td>
</tr>
<tr>
<td>• Grade 3</td>
<td>Temporary dose interruption until recovery to Grade ≤ 1. Re-initiate treatment at 5 mg daily.</td>
</tr>
<tr>
<td>• Grade 4</td>
<td>Discontinue treatment</td>
</tr>
<tr>
<td>Other non-haematological toxicities (excluding metabolic events)</td>
<td>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.</td>
</tr>
<tr>
<td>• Grade 2</td>
<td>Note: 1st occurrence:</td>
</tr>
<tr>
<td>• Grade 3</td>
<td>Temporary dose interruption until recovery to Grade ≤ 1. Re-initiate treatment at 5 mg daily. Consider re-initiating treatment at 5 mg daily.</td>
</tr>
<tr>
<td>• Grade 4</td>
<td>Discontinue treatment</td>
</tr>
<tr>
<td>Metabolic events (e.g. hyperglycaemia, dyslipidaemia)</td>
<td>No dose adjustment required.</td>
</tr>
<tr>
<td>• Grade 2</td>
<td>Temporary dose interruption. Re-initiate treatment at 5 mg daily.</td>
</tr>
<tr>
<td>• Grade 3</td>
<td>Discontinue treatment</td>
</tr>
</tbody>
</table>

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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.

**DRUG INTERACTIONS:**
- Everolimus is a substrate of CYP 3A4 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 CYP 3A4 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.

**ATC CODE:**
Everolimus – L01XE10

**REFERENCES:**
4. Afatinor® Summary of Product Characteristics Accessed April 2018
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

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

1 ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at; http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/