Everolimus and Exemestane Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor.	C50	00322a	N/A

* This applies to post 2012 indications

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 full glass of water	Continuous
Exemestane	25mg daily	PO once daily after food	Continuous
If a dose of everolimus or exemestane 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, exemestane or any of the excipients
- Caution is advised for patients with pre-existing significant lung compromise due to the risk for pneumonitis
- Pregnancy
- Breastfeeding

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
- Blood glucose

Regular tests:

- FBC, renal and liver profile every 4 weeks or as clinically indicated
- Total cholesterol and triglycerides every 4 weeks or as clinically indicated
- 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. Exemestane should be continued regardless of everolimus interruptions or dose modifications**.**

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 and exemestane in renal and hepatic impairment

Drug	**Renal Impairment**	**Hepatic Impairment**	
Everolimus	Renal impairment: no dose adjustment is needed Hemodialysis: no need for dose adjustment is expected	Mild (Child Pugh Class A)	75% of original dose
		Moderate (Child Pugh Class B)	50% of original dose
		Severe (Child Pugh Class C)	25% of original dose
Exemestane	Due to large therapeutic index no dose adjustment is needed Hemodialysis: no need for dose adjustment is expected	Due to large therapeutic index no dose adjustment is needed	
Recommendations for everolimus from Giraud et al 2023 Recommendations for exemestane from Giraud et al 2023			

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 5 mg 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	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	
○ 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
Grading based on National Cancer Institute (NCI) Common Terminolgy Criteria for Adverse Events (CTCAE) v3.0	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting Available on the NCCP website

Everolimus: Minimal to Low (**Refer to local policy).**

For information:
Within NCIS regimens, antiemetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

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:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS:

- **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.
- **Change in bone density:** Exemestane is a potent oestrogen lowering agent, and a reduction in bone mineral density (BMD) and an increased fracture rate have been observed following administration.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

1. Baselga J, Campone M, Piccart M. et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012;366(6):520-529.
2. Yardley DA, Noguchi S, Pritchard, KI. et al. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther 2013;30(10):870-884.
3. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V6 2025. 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
5. Everolimus (Afinitor®) Summary of Product Characteristics.Accessed April 2025. Available at: https://www.ema.europa.eu/en/documents/product-information/afinitor-epar-product-information_en.pdf
6. Exemestane Summary of Product Characteristics. Accessed April 2025. Available at: https://assets.hpra.ie/products/Human/27567/Licence_PA2315-087-001_27042023100604.pdf

Version	Date	Amendment	Approved By
1	03/05/2016		Prof Maccon Keane
2	02/05/2018	Applied new NCCP regimen template and updated dosing for adverse events as per SmPC	Prof Maccon Keane
3	13/05/2020	Update of dose modifications for adverse events and adverse events.	Prof Maccon Keane
4	13/06/2025	Regimen reviewed. Table 2 updated in line with Giraud et al 2023.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.