Everolimus and Exemestane Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	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	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
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			

ELIGIBILTY:

- 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
- 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 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 in renal and hepatic impairment

Drug	**Renal Impairment**	**Hepatic Impairment**	
Everolimus	No dose modification 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.	
Exemestane	No dose modification required	No dose modification required	

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

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
- **Stomatitis:** Stomatitis, including mouth ulceration and oral mucositis, is a common side effect with this treatment and usually occurs within the first 8 weeks of treatment. Early intervention may help to avoid dose alteration or interruption. Topical treatments (alcohol free) are recommended. Monitoring for and treatment of fungal infection is recommended, especially in patients being treated with steroid-based medicinal products. Antifungal agents should not be used unless fungal infection has been diagnosed.
- **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.
- **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:

- 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
Exemestane	-	L02BG06

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. Everolimus (Afatinor®) Summary of Product Characteristics. Last updated: 25/02/2020. Accessed May 2020. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001038/WC500022814.pdf
4. Aromasin Summary of Product Characteristics. Last updated: 26/06/2018. Accessed May 2020. Available at: https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0822-111-001_25062018103042.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

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.