Indication	For the treatment of hormone receptor-positive, HER2 negative advanced breast cancer in postmenopausal women without symptomatic visceral disease previously treated with a non-steroidal aromatase inhibitor. NB: The patient should have received no more than one line of cytotoxic chemotherapy for advanced breast cancer.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 28 days. Continue until progression of disease or unacceptable toxicity.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Monitor FBC, LFT's and U&E's prior to each cycle for 6 months and then where clinically appropriate every 3 months thereafter. • Monitoring of fasting serum glucose should be checked prior to treatment and periodically throughout. • Monitoring of blood cholesterol and triglycerides should be checked prior to treatment and periodically throughout. • 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 (e.g. for one week). If a dose reduction of everolimus is required the suggested dose is 5mg daily. (See table below for details) • Patients treated with exemestane tablets should be carefully monitored and treatment for, or prophylaxis of, osteoporosis should be initiated in at risk patients. • Routine assessment of 25 hydroxy vitamin D levels prior to the start of aromatase inhibitor treatment should be considered, and if there is a deficiency, supplementation with Vitamin D should be given. • **Dose Reduction:** • If dose reduction of everolimus is required, the recommended dose is 5 mg daily and must not be lower than 5 mg daily (see table below). • **Hepatic Impairment:** • Everolimus: A dose reduction to 5mg and 10mg on alternate days daily 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 (Child-Pugh C), only if benefit outweighs risk. • **Renal Impairment:** • No dose reduction of either agent is required in renal impairment however exemestane should be used with caution in patients with renal impairment. • **<u>Adverse reactions:</u>** • Radiation therapy complications o Serious and severe radiation reactions (such as radiation oesophagitis, radiation pneumonitis and radiation skin injury), including fatal cases, have been reported when everolimus was taken during, or shortly after, radiation therapy. Caution should therefore be exercised for the potentiation of radiotherapy toxicity in patients taking everolimus in close temporal relationship with radiation therapy.

	○ Additionally, radiation recall syndrome (RRS) has been reported in patients taking everolimus who had received radiation therapy in the past. In the event of RRS, interrupting or stopping everolimus treatment should be considered. • Non-infectious pneumonitis is a class effect for everolimus; patients should be advised to report promptly any new or worsening respiratory symptoms. • Everolimus has immunosuppressive properties and may pre-dispose patients to bacterial, fungal, viral and protozoan infections including reactivation of hepatitis B. Monitor patients appropriately. • Stomatitis, including mouth ulcerations and oral mucositis, is a commonly reported adverse reaction in patients treated with everolimus. (See KMCC website SACT induced mucositis & stomatitis: http://www.kmcc.nhs.uk/medicines-and-prescribing-incorporating-sact-pathways/sact-pathways-guidelines-for-the-management-of-sact-induced-adverse-reactions-and-nursing/) • Treatment with everolimus may impair wound healing. • **Drug Interactions (for comprehensive list refer to BNF/SPC):** • Avoid concomitant treatment of everolimus with potent CYP3A4/PgP inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, ritonavir and erythromycin) or inducers (e.g. rifampicin, phenytoin, and carbamazepine) - see SPC section 4.5 for more information. • Monitor closely if exemestane is taken with orally administered CYP3A4 substrates with a narrow therapeutic index (e.g. pimozide, terfenadine, astemizole, cisapride, quinidine or ergot alkaloid derivatives). • Use of live vaccines should be avoided during treatment with everolimus. • Patients taking concomitant ACE inhibitor (e.g. ramipril) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment). • Preparations containing St John's Wort should not be used during treatment with everolimus. • Patients should avoid grapefruit juice. • **Driving:** Everolimus and exemestane can potentially cause fatigue and drowsiness in some patients and therefore should be advised to be cautious when driving or using machines. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet.
References	KMCC SACT proforma BRE-030 v3 SPC accessed online 31/01/2022 everolimus and exemestane BNF accessed online 31/01/2022

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1 Dose modifications of everolimus

Adverse reaction	Severity[1]	Everolimus dose adjustment
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	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at same dose. If stomatitis recurs at Grade 2, 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	Temporary dose interruption until recovery to Grade ≤1. 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. Re-initiate treatment at 5 mg daily.
	Grade 4	Discontinue treatment.
Thrombocytopenia	Grade 2 (<75, ≥50x10^9/l)	Temporary dose interruption until recovery to Grade ≤1 (≥75x10^9/l). Re-initiate treatment at same dose.
	Grade 3 & 4 (<50x10^9/l)	Temporary dose interruption until recovery to Grade ≤1 (≥75x10^9/l). Re-initiate treatment at 5 mg daily.
Neutropenia	Grade 2 (≥1x10^9/l)	No dose adjustment required.
	Grade 3 (<1, ≥0.5x10^9/l)	Temporary dose interruption until recovery to Grade ≤2 (≥1x10^9/l). Re-initiate treatment at same dose.
	Grade 4 (<0.5x10^9/l)	Temporary dose interruption until recovery to Grade ≤2 (≥1x10^9/l). Re-initiate treatment at 5 mg daily.
Febrile neutropenia	Grade 3	Temporary dose interruption until recovery to Grade ≤2 (≥1.25x10^9/l) and no fever. 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		

Repeat every 28 days

Day	Drug	Dose	Route	Administration
1	**EVEROLIMUS**	**10mg**	PO	Once daily, swallowed whole with a glass of water. Available as 5mg and 10mg tablets. Dispense 30 days supply.
	EXEMESTANE	**25mg**	PO	Once daily, preferably after a meal.
	Metoclopramide	10mg	PO	10mg TDS when required. Do not take for more than 5 days continuously.
	Loperamide	2mg	PO	Take two initially then one after each loose stool when required (max.8 a day). (dispense one original pack on cycle 1 then only if required)
	Dexamethasone mouthwash (dispense tablets)	0.5mg/5ml	TOPICAL	Dissolve two 500mcg tablets in 10ml of water. Use as mouthwash QDS. **DO NOT SWALLOW.** Cycle 1&2 only and then review.