Everolimus and Exemestane

Indication
Treatment of patients with hormone receptor positive, HER 2 negative advanced breast cancer, in post menopausal patients without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor.

(NICE TA421)

ICD-10 codes
Codes with a prefix C50

Regimen details

Day	Drug	Dose	Route
1-28*	Everolimus	10mg OD	PO
1-28*	Exemestane	25mg OD	PO

*Continuous treatment

Cycle frequency
28 days - continuous

Number of cycles
Continue until disease progression or unacceptable toxicity.

Administration
Everolimus is available as 2.5mg, 5mg and 10mg tablets.
Everolimus should be swallowed whole with a glass of water at the same time each day, either with or without food, but not after a high fat meal.
If a dose is missed by more than 12 hours or the patient vomits after taking their dose, the patient **should not** take an additional dose. The patient should take the usual prescribed dose on the following day.

Grapefruit and grapefruit juice should be **avoided** whilst taking everolimus.

Exemestane is available as 25 mg tablets and should be taken after food.

Pre-medication
Nil

Emetogenicity
This regimen has mild emetic potential (no routine anti-emetics required)

Additional supportive medication
Mouthwashes as per local policy.

Extravasation
N/A

Investigations - pre first cycle

Investigation	Validity period
FBC	7 days
U+E (including creatinine)	7 days
LFTs	7 days
Glucose	7 days
Lipids	7 days
Blood pressure	Must be controlled before initiating everolimus

ECG if patient has significant cardiac history.

Investigations – pre subsequent cycles

Patients should be reviewed every 4 weeks for the first 3 cycles. This may be increased to every 8 weeks if stable.

Investigation	Validity period
FBC	7 days
U+E (including creatinine)	7 days
LFTs	7 days
Glucose	Every 6-8 weeks then as clinically indicated
Lipids	Every 6-8 weeks then as clinically indicated

ECG if patient has significant cardiac history.
CXR every 8 weeks or as per symptoms at the consultants discretion.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Bilirubin	≤ ULN
Creatinine Clearance	> 30mL/min

Dose modifications

- **Haematological toxicity**

Toxicity	Definition	Dose adjustment
Neutropenia	Neutrophils 0.5 - < 1.0 x 10^9/L	1st occurrence: Delay until ≥ 1.0 x 10^9/L then continue at same dose 2nd occurrence: Delay until ≥ 1.0 x 10^9/L then continue at 5mg OD 3rd occurrence: Discontinue
	Neutrophils <0.5 x 10^9/L	1st occurrence: Delay until ≥ 1.0 x 10^9/L then continue at 5mg OD 2nd occurrence: Discontinue
Thrombocytopenia	Platelets 50-75 x 10^9/L	1st occurrence: Delay until recovery then continue at same dose 2nd occurrence: Delay until recovery then continue at 5mg OD 3rd occurrence: Discontinue
	Platelets 25-49 x 10^9/L	1st occurrence: Delay until recovery then continue at 5mg OD 2nd occurrence: Discontinue
	Platelets <25 x 10^9/L	Discontinue

- **Renal impairment**

No dose modifications are required in renal impairment.
Cases of renal failure have been reported in patients receiving everolimus. Renal function should be monitored. Patients with acute renal failure should stop treatment until the cause has been investigated and treated.

- **Hepatic impairment**

Everolimus is mainly excreted via hepatic elimination. Doses adjustments should be made as per table below if patient's hepatic status changes during treatment.

Degree of hepatic impairment	**Everolimus dose**
Mild (Child Pugh A)	7.5mg OD
Moderate (Child Pugh B)	5mg OD
Severe (Child Pugh C)	Not recommended – if used dose must not exceed 2.5mg OD

Child Pugh Classification:

Score	1	2	3
Bilirubin (µmol/L)	<34	34-50	>50
Albumin (g/L)	>35	28-35	<28
PT (s prolonged)	<4	4-6	>6
Encephalopathy	none	mild	marked
Ascites	none	mild	marked

The individual scores are summed and then grouped as:

- <7 = A
- 7-9 = B
- >9 = C

- **Other toxicities**

Toxicity	Definition	Dose adjustment
Non-infectious pneumonitis	Grade 1	100%
	Grade 2	If symptomatic withhold treatment. Resume at 5mg dose when symptoms resolve to ≤ Grade 1 Discontinue if symptoms do not resolve within 4 weeks.
	Grade 3	Withhold treatment until ≤ Grade 1 May resume at 5mg dose if evidence of clinical benefit. If grade 3 toxicity recurs discontinue.
	Grade 4	Discontinue
Stomatitis	Grade 1	100%
	Grade 2	Withhold treatment until ≤ Grade 1 Resume at same dose If recurs at Grade 2, withhold treatment until ≤ Grade 1 and resume at 5mg dose.
	Grade 3	Withhold treatment until ≤ Grade 1 Resume at 5mg dose
	Grade 4	Discontinue
Other non-haematological toxicity (except alopecia and metabolic events)	Grade 1	100%
	Grade 2	If toxicity is tolerable, no dose modification required. If intolerable withhold treatment until ≤ Grade 1 and resume at same dose If recurs at Grade 2, withhold treatment until ≤ Grade 1 and resume at 5mg dose.
	Grade 3	Withhold treatment until ≤ Grade 1 Resume at 5mg dose. If grade 3 toxicity recurs discontinue.
	Grade 4	Discontinue
Metabolic events (hyperglycaemia, dyslipidaemia)	Grade 1 or 2	100%
	Recurrent Grade 2 or Grade 3	Withhold treatment and resume at 5mg dose
	Recurrent Grade 3 or Grade 4	Discontinue

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Cardiotoxicity
Venous thromboembolism
Impaired wound healing
Teratogenicity
Infertility (males)
ARDS

- **Frequently occurring side effects**

Diarrhoea
Nausea and vomiting
Hyperlipidaemia
Myelosuppression
Rash
Pneumonitis (patients should report any new or worsening respiratory symptoms)
Stomatitis/Mucositis
Hyperglycaemia

- **Other side effects**

Taste disturbances
Fatigue
Headache
Insomnia
Weight loss

Significant drug interactions – for full details consult product literature/ reference texts

CYP3A4 inhibitors (e.g. ketoconazole, voriconazole, clarithromycin, ritonavir): avoid co-administration these may increase plasma concentrations of everolimus. Risk of toxicity.

Grapefruit and grapefruit juice: avoid as an inhibitor of CYP3A4 and may increase plasma concentrations of everolimus.

Inducers of CYP3A4 (e.g. rifampicin, phenytoin, carbamazepine, St Johns Wort): avoid co-administration as these may reduce exposure to everolimus. Risk of therapeutic failure.

ACE inhibitors: caution, increased risk of angioedema

Additional comments

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take everolius.

References

- Baselga et al. Everolimus in Postmenopausal Hormone-Receptor-Positive Advanced Breast Cancer. *N Engl J Med* 2012;366:520-9.
- Summary of Product Characteristics Everolimus - Afinitor®(Novartis) accessed 1 May 2019 available at www.medicines.org.uk
- Summary of Product Characteristics Exemestane accessed 1 May 2019 available at www.medicines.org.uk

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