**Systemic Anti Cancer Treatment Protocol**

# EVEROLIMUS AND EXEMESTANE

**PROTOCOL REF: MPHAEVEXBR**
**(Version No: 1.0)**

## Approved for use in:

Postmenopausal women with ER positive, HER2 negative advanced breast cancer

No symptomatic visceral disease

Following progression/recurrence after non-steroidal aromatase inhibitor

Requires blueteq registration

## Dosage:

| Drug | Dosage | Route | Frequency |
|---|---|---|---|
| Everolimus | 10mg daily | Oral | Continuous, supply will be every 28 days |
| Exemestane | 25mg daily | Oral | Continuous, supply will be via GP |

Treatment is continuous until disease progression or unacceptable toxicity. If everolimus is discontinued due to toxicity then exemestane can continue.

## Extravasation risk:

Not applicable

## Administration:

Everolimus should be administered orally once daily at the same time every day, consistently either with or without food.

Everolimus tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed.

**Drug Interactions**

Everolimus is metabolized by the cytochrome CYP3A4 pathway and therefore drugs that induce or inhibit this enzyme should be avoided where possible.

**INDUCERS (lowers everolimus levels):** Carbamazepine, phenobarbital, phenytoin, dexamethasone, rifabutin, rifampicin, St John's Wort, troglitazone, pioglitazone

**INHIBITORS (increases everolimus levels):** Indinavir, nelfinavir, ritonavir, clarithromycin, erythromycin, itraconazole, ketoconazole, nefazodone, grapefruit juice, verapamil, diltiazem, cimetidine, amiodarone, fluvoxamine, mibefradil

ACE inhibitors – concomitant use increases risk for angioedema.

## Main Toxicities (everolimus):

Note: exemestane side effects not included

| | |
|---|---|
| **Haematological** | Neutropenia, anaemia, thrombocytopenia, |
| **Gastrointestinal** | Nausea, vomiting, diarrhoea, mucositis |
| **Respiratory** | Pneumonitis, dyspnoea |
| **Hepatobiliary** | Elevation of liver transaminases, alkaline phosphatase and bilirubin. |
| **Skin and subcutaneous tissue disorders** | Skin rash<br>Oedema |
| **General disorders and administration site conditions** | Hyperglycaemia<br>Headaches<br>Infertility, early menopause |

## Investigations:

| | Pre | C1 D1 | C2 D1 | C3 D1 | C4 D1 | C5 D1 | Ongoing |
|---|---|---|---|---|---|---|---|
| Medical Assessment | X | X | X | X | X | X | |
| Nursing Assessment | | X | X | X | X | X | Every cycle |
| FBC | X | | X | X | X | X | Every cycle |
| U&E & LFT | X | | X | X | X | X | Every cycle |
| Fasting lipids and cholesterol | X | | | X | | X | Every 12 weeks |
| CT scan | X | | | | X | | Every 12 weeks |
| Informed Consent | X | | | | | | |
| PS recorded | X | X | X | X | X | X | |
| Toxicities documented | X | X | X | X | X | X | |
| Weight recorded | X | X | X | X | X | X | Every cycle |
| Random glucose | X | | X | X | X | X | Every 4 weeks |

## Dose Modifications and Toxicity Management

### Haematological toxicity

Proceed on day 1 if:-

| | |
|---|---|
| ANC ≥ 1.0 x $10^9$/L | Platelets > 75 x $10^9$/L |

If platelets 50 to 75 x $10^9$/L, and/or neutrophils 0.5 to 1.0 x $10^9$/L then interrupt treatment until recovered to > 75 x $10^9$/L and > 1.0 x $10^9$/L and re-initiate at previous dose.

If below these levels then re-initiate at reduced dose of 5mg daily.

## Non-haematological toxicity

| | |
|---|---|
| Stomatitis | For Grade 2 toxicity:<br>Temporary dose interruption until recovery to Grade ≤1.<br>Re-initiate Everolimus at same dose. Prescribe steroid mouthwash (prednisolone soluble 10mg four times daily, not swallowed)<br><br>If stomatitis recurs at Grade 2 or first occurrence at Grade 3, interrupt dose until recovery to Grade ≤1. Re-initiate Everolimus at 5 mg daily.<br><br>Grade 4 toxicity: discontinue |
| Metabolic events | Hyperglycaemia, dyslipidaemia (including hypercholesterolaemia and hypertriglyceridaemia) occur. Monitoring of blood glucose, blood cholesterol and triglycerides prior to the start of everolimus therapy and periodically thereafter, as well as management with appropriate medical therapy, is recommended.<br><br>Grade 1 and 2 – no dose adjustment required.<br>Grade 3: Temporary dose interruption.<br>Re-initiate everolimus at 5 mg daily.<br>Grade 4: Discontinue |
| Non-infectious pneumonitis | Grade 2: Consider interruption of therapy until symptoms improve to Grade ≤1. And commence systemic corticosteroids.<br>Re-initiate everolimus at 5 mg daily.<br>Discontinue treatment if failure to recover within 4 weeks.<br><br>Grade 3: Interrupt everolimus until symptoms resolve to Grade ≤1.<br>Consider re-initiating at 5mg daily, but if toxicity recurs at G3 then discontinue<br>Grade 4: Discontinue |
| Other non-haematological toxicities | Grade 1 and Grade 2 tolerable: no dose adjustment required.<br>Grade 2 intolerable: Temporary dose interruption until recovery to Grade ≤1. Re-initiate Everolimus at same dose.<br>If toxicity recurs then dose reduce to 5mg daily.<br>Grade 3: As above, with re-initiation at 5mg daily.<br>Grade 4: Discontinue |

## Hepatic function

Mild hepatic impairment – recommended starting dose is 7.5mg daily

Moderate hepatic impairment – recommended starting dose is 5mg daily

**Renal function**

No adjustments required

Elevations of serum creatinine, usually mild, and proteinuria have been reported

## References:

NICE TA421 Dec 2016

BOLERO-2: Everolimus in postmenopausal hormone receptor positive advanced breast cancer

Baselga et al NEJM 2012 366:520-529