EVEROLIMUS (AFINITOR ®)

NHS Northern Cancer Alliance

DRUG ADMINISTRATION SCHEDULE

Day	Cycle length	Drug	Daily Dose	Route	Schedule
Days 1 to 28	4 weeks	**Everolimus**	10 mg	Oral	ONCE daily

In Breast cancer

Days 1 to 28	4 weeks	**Exemestane**	25 mg	Oral	ONCE daily

- Everolimus is available as 2.5mg, 5mg and 10mg tablets, which should be taken as the same time of day every day, consistently with or without food, but not after a high fat meal.
- Grapefruit and grapefruit juice should be avoided while on everolimus.
- Swallowed whole with a glass of water.

NUMBER OF DAYS PER CYCLE

28 Days. The recommended dose is 10 mg everolimus once daily continuously. One cycle equals 4 weeks (28 days) of treatment. Treatment should continue for as long as clinical benefit is observed or until unacceptable toxicity occurs.

APPROVED INDICATIONS

Breast in combination

Everolimus, in combination with **Exemestane 25mg oral once daily**, is recommended as an option for treating advanced human epidermal growth factor receptor 2 (HER2)-negative, hormone-receptor-positive breast cancer in postmenopausal women without symptomatic visceral disease that has recurred or progressed after a non-steroidal aromatase inhibitor.

Renal Cell Carcinoma (single agent)

Everolimus is recommended as an option for treating advanced renal cell carcinoma that has progressed during or after treatment with vascular endothelial growth factor therapy.

Neuroendocrine tumours (including pancreatic neuroendocrine tumours)

Everolimus is recommended, within its marketing authorisations, as options for treating well- or moderately differentiated unresectable or metastatic neuroendocrine tumours (NETs) of pancreatic origin in adults with progressive disease.

Everolimus is recommended, within its marketing authorisation, as an option for treating well-differentiated (grade 1 or grade 2) non-functional unresectable or metastatic NETs of gastrointestinal or lung origin in adults with progressive disease.

ELIGIABILITY CRITERIA

For patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate haematological, coagulation, hepatic, renal, and cardiac function.

PREMEDICATION: None

RECOMMENDED TAKE HOME MEDICATION

Metoclopramide 10 three times daily as required
Loperamide 2mg prn (max 16mg in 24 hours) for diarrhoea as required
Emollients (for skin rash) as required
Mouthcare – an alcohol-free corticosteroid mouthwash (as per local policy) may decrease the incidence and severity of stomatitis.

Suggested antiemetic regimen - may vary with local practice. See CINV policy for more details

INVESTIGATIONS / MONITORING REQUIRED

- Baseline assessment of BP and cardiac function for patients with cardiac risk factors or history of coronary artery disease
- FBC, U&E, LFT's & tumour markers as appropriate prior to each cycle
- Baseline CXR and CXR after every other cycle if suspected pneumonitis (see administration noted and toxicity management sections below)
- Cholesterol, triglycerides, urinary protein, fasting blood glucose prior to treatment and periodically thereafter

REVIEW BY CLINICIAN

Day 28 of each cycle as appropriate

NURSE / PHARMACIST LED REVIEW

Each cycle as applicable according to local protocols

ADMINISTRATION NOTES

Because of the risk 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, consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Everolimus may be re-initiated at 5 mg daily.
For cases where symptoms of non-infectious pneumonitis are severe, everolimus therapy should be discontinued and the use of corticosteroids may be indicated until clinical symptoms resolve.

Everolimus is a substrate of CYP3A4, and a substrate and moderate inhibitor of PgP. Therefore, absorption and subsequent elimination of everolimus may be influenced by products that affect CYP3A4 and/or PgP.

- Drugs that are CYP3A4 inhibitors such as ketoconazole, and to a lesser extent itraconazole, erythromycin, clarithromycin and grapefruit juice may decrease metabolism and increase sunitinib plasma concentrations. If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, dose reduction to 5 mg daily or 5 mg every other day may be considered.
- Drugs that are CYP3A4 inducers such as rifampicin, dexamethasone, phenytoin, carbamazepine, phenobarbital or Hypericum perforatum (St John's Wort) may increase metabolism and decrease sunitinib plasma concentrations. A dose increase of everolimus from 10 mg daily up to 20 mg daily should be considered using 5 mg increments applied on Day 4 and 8 following start of the inducer.
- The immune response to vaccination may be affected and, therefore, vaccination may be less effective during treatment with everolimus. The use of live vaccines should be avoided during treatment with everolimus

TOXICITIES

- GI (stomatitis, diarrhoea, nausea)
- Anaemia
- Rash, pruritus
- Fatigue
- Infection, including opportunistic (may be severe)
- Anorexia
- Cough, dyspnoea, pneumonitis
- Hypercholesterolaemia, hypertriglyceridaemia
- Decreased calcium, phosphate
- Hyperglycaemia
- Rarely: Congestive heart failure, Haemorrhage, Impaired wound healing

DOSE MODIFICATION

Haematological toxicity

Dose delay: If ANC < 1.0 or Platelets < 75. Until counts recovered. If second episode of dose delay due to reduced counts occurs reduce dose to 5mg, if still not tolerated reduce to 5mg every other day.

Non-Haematological Toxicity, e.g. Diarrhoea, Skin Rash

CTC grade 0 - 1	No change.
CTC grade 2	Therapy withheld until toxicity resolves to grade 1. No change in subsequent dose.
CTC grade 3 - 4	Therapy withheld until toxicity resolves to grade 1. Decrease subsequent dose to 5mg. Dose reduction maintained for ongoing cycle and remainder of therapy.

Management of non-infectious pneumonitis

Grade 1	No specific therapy is required.
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.

TREATMENT LOCATION

Cancer Centre or Cancer Unit with appropriate site specialist.

REFERENCES:

1. Novartis. Summary of Product Characteristics – Afinitor. October 2010.
2. Yao J, Shah M, Ito T, et al. A randomized, double-blind, placebo-controlled, multicenter phase III trial of everolimus in patients with advanced pancreatic neuroendocrine tumors (PNET) (RADIANT-3). New England Journal of Medicine, 364, February 2011, 514-523

DOCUMENT CONTROL

Document Title:	Everolimus protocol CRP11 U003 v5		
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Reviewer:	Chris Beck Chemotherapy Pharmacist Northern Cancer Alliance	**Date Approved:**	28.02.18
Approved by:	Steve Williamson Consultant Pharmacist Northern Cancer Alliance	**Due for Review**	01.03.21
Summary of Changes	1.1	Protocol reviewed. Typing errors corrected	
	2	Added breast and PNETs	
	3.1	Protocol reviewed and reissued, Antiemetic advice updated	
	4.0	Updated with new CDF indication following 12th March changes	
	5.0	Updated with NICE indication, toxicities updated	