Everolimus for the Treatment of Advanced Breast Cancer and Safety Update

National Drug Monograph Addendum

March, 2015

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

This addendum provides information on the use of everolimus for the treatment of advanced breast cancer in postmenopausal women with hormone receptor-positive, HER2-negative disease in combination with exemestane, as well as an update on warning/precaution information added to the prescribing information. The original drug monograph can be found at:

https://vaww.cmopnational.va.gov/cmop/PBM/Clinical%20Guidance/Drug%20Monographs/Everolimus%20Drug%20Monograph.doc

Introduction[1]

Everolimus received initial FDA approval in 2009 for the treatment of patients with advanced Renal Cell Carcinoma after failure of treatment with sunitinib or sorafenib. The drug received FDA approval for the treatment of patients with Subependymal Giant Cell Astrocytoma (SEGA) associated with tuberous sclerosis (TS) who require treatment but are not surgical candidates in 2010. Approval for the treatment of adults with progressive neuroendocrine tumors of pancreatic origin (PNET) was obtained in 2010 as well. FDA approval in advanced breast cancer was granted in 2012.

Background

Purpose for review

FDA-approval for breast cancer indication

Issues to be determined:
Does everolimus offer advantages to currently available alternatives?
What safety issues need to be considered in a Veteran population?

Other therapeutic options

Everolimus is indicated as a second-line hormonal therapy in postmenopausal women with advanced HR+, HER2-negative disease in combination with exemestane after failure of treatment with non-steroidal aromatase inhibitors (letrozole or anastrozole). Therapeutic alternatives would be those hormonal therapies with second-line activity post-aromatase inhibitor and include estrogen receptor antagonists (fulvestrant) or selective estrogen receptor modifiers (tamoxifen).

Formulary Alternatives	Other Considerations
Anastrazole	ORR 12% Daily PO formulation
Letrozole	ORR 19% Daily PO formulation
Tamoxifen	ORR 10%; CBR 40% Daily PO formulation
Non-formulary Alternative (if applicable)	**Other Considerations**
Exemestane	ORR 2-26%; CBR 12-55%; PFS 4 months; Daily PO formulation

Fulvestrant	PFS 4.8 months Monthly IM injection
Exemestane + everolimus	PFS 7 months; ORR 9.5% Daily PO formulation
Tamoxifen + everolimus	TTP 9 months; ORR 14% Daily PO formulation

Clinical Benefit Rate (CBR) - ORR + SD ≥ 6 months

Drug Interactions

Drug-Drug Interactions

Everolimus is a substrate of CYP3A4. It is also a substrate and moderate inhibitor of multidrug efflux pump, PgP

- Co-administration of strong CYP3A4/PgP inhibitors should be avoided as they may result in a significant increase in everolimus exposure.
- Denosumab may enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased.
- Everolimus dose should be reduced when co-administered with a moderate CYP3A4/PgP inhibitor.
  - Erythromycin ↑ C_{max} by 2.0 fold; ↑ AUC by 4.4 fold
  - Verapamil ↑ C_{max} by 2.3 fold; ↑ AUC by 3.5 fold
- Everolimus dose should be increased when co-administered with a strong CYP3A4/PgP inducer.
  - Rifampin ↓ by 63% and C_{max} by 58%
  - St. John's Wort may reduce everolimus exposure unpredictably, therefore should be avoided
- **Drug concentrations that may be altered by everolimus co-administration**
  - ↑ oral midazolam C_{max} by 25%
  - ↑ exemestane C_{min} by 45% and C_{2h} by 64%, although steady state estradiol levels at 4 weeks were not different and there was no increase in adverse events related to exemestane
  - ↑ depot octreotide increased octreotide C_{min} by 50%
  - risk of angioedema may be ↑ with co-administration of ACE-inhibitors

Drug-food Interactions

- Grapefruit juice may increase levels of everolimus therefore patients should avoid grapefruit products.
- Absorption with food may be variable. Take with or without food, but be consistent with regard to food.

Dosing and Administration[1]

The recommended dose of everolimus is 10 mg by mouth once daily, at the same time each day. Dose should be administered in a consistent fashion, with or without food. Everolimus tablets should be taken with a glass of water and should not be crushed or broken.

Treatment should continue until evidence of disease progression or unmanageable toxicity.
Everolimus tablets are available as: 2.5 mg, 5 mg, 7.5 mg and 10 mg tablets (no score).

Refer to Table 1 for dose-adjustment and toxicity management recommendations.

Table 1. Dose Adjustments/Management Recommendations for Adverse Reactions

Adverse reaction	Severity	Dose adjustment/management
Non-infectious pneumonitis	Gr1: asymptomatic, radiographic findings only	No adjustment required; initiate appropriate monitoring
	Gr2: symptomatic, not interfering with ADL	Consider interruption of therapy, R/O infection, consider corticosteroids until symptoms improve to ≤ Gr1; re-initiate drug at lower dose; D/C drug if fail to recover within 4 weeks

	Gr3: symptomatic, interferes with ADL, O2 indicated	Interrupt therapy until symptoms resolve to ≤ Gr1; R/O infection, consider corticosteroids; consider re-initiate drug at lower dose; if toxicity recurs at Gr3, consider D/C
	Gr4: life-threatening, ventilator support indicated	D/C everolimus, R/O infection, consider treatment with corticosteroids
Stomatitis	Gr1: minimal symptoms; normal diet	No dose adjustment required; Manage with non-alcoholic or salt water (0.9%) mouth wash several times per day
	Gr2: symptomatic but can eat & swallow modified diet	Temporary dose interruption until recovery to Gr≤ 1; re-initiate drug at the same dose. If stomatitis recurs at Gr2, interrupt dose until recovery to Gr≤ 1; re-initiate drug at a lower dose. Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste)[ref]
	Gr3: symptomatic & unable to adequately aliment or hydrate orally	Temporary dose interruption until recovery to Gr≤ 1; re-initiate drug at a lower dose. Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste)[ref]
	Gr4: symptoms assoc with life-threatening consequences	D/C everolimus and treat with appropriate medical therapy
Other non-hematologic toxicities (excluding metabolic events)	Gr1	If toxicity is tolerable, no dose adjustment required; initiate appropriate medical therapy and monitor
	Gr2	If toxicity is tolerable, no dose adjustment required; initiate appropriate medical therapy and monitor If toxicity becomes intolerable, temporary dose interruption until recovery to Gr≤ 1; reinitiate drug at same dose If toxicity recurs at Gr2, interrupt drug until recovery to Gr≤ 1; reinitiate drug at a lower dose
	Gr3	Temporary dose interruption until recovery to Gr≤ 1; initiate appropriate medical therapy and monitor; Consider reinitiating drug at a lower dose; if toxicity recurs at Gr3, consider D/C
	Gr4	D/C everolimus and treat with appropriate medical therapy
Metabolic events (e.g. hyperglycemia, dyslipidemia)	Gr1	No dose adjustment required; initiate appropriate medical therapy and monitor
	Gr2	No dose adjustment required; manage with appropriate medical therapy and monitor
	Gr3	Temporary dose interruption; reinitiate drug at a lower dose; manage with appropriate medical therapy and monitor
	Gr4	D/C everolimus and treat with appropriate medical therapy

Warning and Precautions of the Prescribing Information have been updated. Table 2 summarizes the latest information.

Table 2. Warnings and Precautions

Non-infectious Pneumonitis	• Non-infectious pneumonitis is a class effect of rapamycin derivatives. Non-infectious pneumonitis was reported in up to 19% of patients treated with everolimus in the clinical trial setting; Incidence of Gr3 toxicity was up to 4%; Gr4 toxicity was up to 0.2%. • Consider diagnosis of non-infectious pneumonitis if patients present with non-specific respiratory signs/symptoms and infectious, neoplastic and other causes

	have been R/O. • Opportunistic infections such as pneumocystic jiroveci pneumonia (PJP) should be considered in differential diagnosis. • Advise patients to promptly report new or worsening respiratory symptoms. • Radiological changes without respiratory symptomatology, everolimus may continue; imaging appears to overestimate the incidence of clinical pneumonitis. • If respiratory symptoms are moderate, consider dose interruption until they resolve; corticosteroids may be indicated; everolimus may be restarted at 50% lower daily dose. • If Gr3 pneumonitis, interrupt everolimus until resolution Gr $\leq$ 1; reintroduce at 50% lower daily dose. If recurrent Gr3 toxicity, consider D/C everolimus. • If Gr4 pneumonitis, D/C everolimus; corticosteroids may be indicated until symptoms resolve. • Consider PJP prophylaxis for patients requiring the use of corticosteroid treatment. • Pneumonitis has been reported to develop, even at reduced doses.
Infections	• Everolimus is immunosuppressive and may predispose patients to bacterial, fungal, viral or protozoal infections, including opportunistic infections. • Viral infections including reactivation of hepatitis B virus has occurred in patients taking everolimus; some infections have been severe or fatal. • Patients with pre-existing fungal infections should be completely treated prior to starting therapy. • Monitor for signs/symptoms of infection during therapy. Treat infection appropriately and consider interruption or D/C everolimus. • D/C everolimus if a diagnosis of invasive systemic fungal infection is made; PJP, with fatal outcome has been reported, which may be associated with concomitant corticosteroids or other immune-suppressive agents. • PJP prophylaxis should be considered when concomitant corticosteroids or other immune-suppressive agents are required.
Oral Ulceration	• The incidence of mouth ulcers, stomatitis and oral mucositis ranges from 44-78% among clinical trials; Gr3 or Gr4 stomatitis was reported in 4-9%. • Avoid alcohol-, hydrogen peroxide-, iodine- or thyme-containing mouthwashes as they may exacerbate the condition; antifungal agents should only be used in the diagnosis of a fungal infection.
Renal Failure	• Cases of renal failure, some with fatal outcome, have been noted in clinical trials with everolimus.
Impaired Wound Healing	• Everolimus may delayed wound healing and increase wound-related complications like dehiscence, infection, etc. Some complications may require surgical intervention. • Use caution when using everolimus in the peri-surgical period.
Geriatric Patients	• In the breast cancer trial, there was a higher incidence of deaths due to any cause in the 28-days post last dose of everolimus which was higher in geriatric patients: 6% in those age $\geq$ 65 years vs. 2% in those age < 65 years. • Monitoring and appropriate dose adjustments for adverse reactions are recommended.
Laboratory Tests & Monitoring	• *Renal function.* Serum creatinine elevations and proteinuria have been reported; monitoring of BUN, urinary protein or serum creatinine is recommended prior to the start of everolimus and periodically throughout the course of therapy; pay particular attention to patients with additional risk factors that may further alter renal function. • *Blood Glucose & Lipids.* Hyperglycemia, hyperlipidemia and hypertriglyceridemia have been reported; Prior to the start of everolimus, monitor fasting serum glucose and lipid profile; Monitor periodically throughout therapy and initial appropriate

	medical management as needed; optimize blood glucose and lipids prior to starting everolimus, if possible. • *Hematologic Parameters.* Decreased hemoglobin, lymphocytes, neutrophils and platelets have been reported in patients taking everolimus; monitor complete blood count prior to therapy initiation and periodically during therapy. • *Hepatic Impairment.* Everolimus exposure increases in patients with hepatic impairment. In patients with breast cancer and severe hepatic impairment (Child-Pugh class C), if benefits outweighs risk, drug can be given at reduced dose of 2.5 mg daily. Those with mild hepatic impairment (Child-Pugh class A) the recommended dose is 7.5 mg daily with further reduction to 5 mg daily if not tolerated. Those with moderate hepatic impairment (Child-Pugh class B) can take the recommended 5 mg daily dose, with reduction to 2.5 mg daily based on tolerance. • *Embryo-Fetal Toxicity.* Everolimus can cause fetal harm based on evidence of embryo-fetal toxicity noted among animals exposed to less than human doses. Patients should be informed of the potential hazard to a fetus, if they should become pregnant while taking everolimus. Advise female patients of child-bearing potential that they should avoid becoming pregnant and use highly effective contraception during therapy and for up to 8 weeks after completion of treatment. • *Pneumonitis: Oxygen Saturation:* Baseline oxygen saturation by pulse oximetry and after that as needed for symptoms. • *Fatigue and loss of appetite:* Monitor baseline fatigue and nutrition with any consistent instrument and follow periodically

Review of Efficacy

Everolimus + exemestane

Study design	Inclusion/Demographics	Intervention	Outcomes
BOLERO-2[2] R, DB, MC, PC, P3 N=724 189 centers; 24 countries	Inclusion Postmenopausal women; ER+, HER2-neg Advanced BrCa with recurrence or PD post-therapy with letrozole or anastrazole in adjuvant or advanced setting; ≥1 measurable or bone lesion ECOG PS 0-2 Exclusion Brain mets Prior exemestane or mTOR inhibitors Median age 62 yrs (28-93) 56% visceral disease 76% bone mets 84% hormone sensitive 79-84% adv/metastatic disease Median 3 prior therapies Prior therapy: Letrozole or anastrazole 100% Tamoxifen 48% Fulvestrant 16% Chemotherapy 68%	Everolimus + exemestane (E+E) vs. Placebo + exemestane (P+E) Rand 2:1 ratio Everolimus 10mg PO daily Exemestane 25 mg PO daily Stratified by prior hormone sensitivity; visceral metastasis Tumor assessment q6wks to PD	Everolimus + exemestane (E+E) vs. Placebo + exemestane (P+E) Primary endpoint: PFS Secondary: OS, ORR, safety, QoL Median PFS: 10.6 vs. 4.1 mos [HR 0.36(95% CI: 0.27-0.47); p<0.001] ORR 12.6 vs. 1.7% After median follow-up 39 months, No diff OS [HR 0.89(0.73-1.10)] SAE (Gr3, Gr4) SAE 23 vs. 12% Stomatitis 8 vs. 1%; Anemia 6 vs. 1%; Dyspnea 4 vs. 1%; Fatigue 4 vs. 1%; Pneumonitis 3 vs. 0%; Hyperglycemia 4 vs. <1% ↑ LFTs 3% D/C due to AE: 19 vs. 4% Deaths due to tx: 7 (1%) vs. 1 (<1%) ↓ECOG PS: no difference

Refractory, defined as recurrence during or within 12 months after the end of adjuvant treatment or progression during or within 1 month after end of treatment for advanced disease.

- Results of BOLERO-2 showed that the combination of exemestane + everolimus improved activity and PFS compared to exemestane alone. A positive impact on overall survival has not been shown.
- The toxicity profile of the combination warrants extreme caution and intense monitoring throughout therapy. Adverse events led to a high discontinuation rate in the treatment arm.
- Deaths thought to be attributable to active treatment were greater among elderly patients than in the placebo arm.
- A positive impact on quality of life with the combination has not been shown; results indicate that the decline in ECOG PS was not significantly different than the exemestane alone arm.
- NCCN guidelines include the combination of everolimus + exemestane as a treatment option in postmenopausal women as subsequent endocrine therapy for systemic disease with a category 2A recommendation, noting that consideration can be given to this combination in patients who meet BOLERO-2 eligibility criteria.

Everolimus + tamoxifen (off-label)

Study design	Inclusion/Demographics	Intervention	Outcomes
GINECO[3] MC, OL, P2 N=111	Inclusion Postmenopausal women; ER+, HER2-neg metastatic BrCa with recurrence or PD post-therapy with AI in adjuvant or advanced setting; ≥1 measurable or bone lesion ECOG PS 0-2 Exclusion Brain mets Prior TAM allowed in adjuvant setting Median age 64 yrs More ECOG PS 0 in TAM/ever arm Med duration metastatic disease 1.2 years; 78% bone mets 53% visceral mets; Prior adjuvant AI 41% Prior AI 67% 1st-line mBC tx Primary resistance 49% Secondary 51%	Tamoxifen (TAM) 20mg daily vs. TAM + everolimus 10mg daily Rand 1:1 ratio Everolimus 10mg PO daily Exemestane 25 mg PO daily Stratified by primary vs. secondary resistance Primary= relapse w/in 6 mos of tx Secondary= relapse > 6 mos Treat until PD, toxicity or pt decision Tumor assessment q2 months until 6-mos visit, then q3 months until 18-mos	Tamoxifen (TAM) 20mg daily vs. TAM + everolimus 10mg daily Primary endpoint: CBR Secondary: TTP, OS, ORR, safety Median follow-up at 24 mos Med treatment duration: 4.8 vs. 6.2 mos CBR at 6 mos (ITT): 42 vs. 61%; p=0.045 CBR in Primary resistance: 36 vs. 46% CBR in Secondary resistance: 48 vs. 74% RR in Measurable disease: 13 vs. 14% TTP 4.5 vs. 8.6 mos Median OS: 33 mos vs. NR AE all (Gr 3,4) Fatigue 72 (9) vs. 53 (17)%; Stomatitis 56 (17) vs. 7 (0)%; Rash 44 (6) vs. 7 (0)% Anorexia 43 (11) vs. 18 (6)% Diarrhea 39 (3) vs. 11 (0)% SAEs: 32% in each group D/C due to AE: 7 vs. 22%

CBR (clinical benefit rate)- Defined as % all patients with CR or PR or SD at 6 months

- The combination of everolimus + tamoxifen is active in postmenopausal women, HR+, HER2-negative metastatic breast cancer. Improvement in clinical benefit rate was greater in the everolimus + tamoxifen arm, with greater impact among those patients with secondary resistance.
- A greater toxicity profile was noted in the everolimus + tamoxifen arm, leading to more treatment discontinuations.
- Quality of life was not formally assessed in this trial.

Projected Place in Therapy

Among postmenopausal women with hormone receptor positive disease, aromatase inhibitors are considered a standard as first-line therapy. Patients who do not respond to first-line therapy, or develop resistance, are in need of second-line options. The current endocrine options for the second-line setting include other aromatase inhibitors and estrogen antagonists, such as fulvestrant and tamoxifen.

One mechanism of endocrine resistance involves the activation of mammalian target of rapamycin (mTOR) signal transduction pathway.

The combination of everolimus + exemestane showed an improvement in PFS and ORR compared to exemestane alone. No difference in OS has been reported.

The incidence Grade 3, 4 toxicities was greater in the combination of everolimus + exemestane, resulting in a higher discontinuation rate. Dose interruptions or reductions in dose were needed in a large percentage of patients receiving the combination. Of note, drug-related deaths among patients aged 65 years and older were also greater in the combination arm. The toxicity profile of this combination warrants great consideration for use in the Veteran population, as it is likely that those eligible for the combination of everolimus + exemestane, may be geriatric patients.

References

1. Everolimus (Afinitor®) Prescribing Information. Novartis Pharma Stein AG. Stein, Switzerland.

2. Baselga J, Campone M, Piccart, et al. Everolimus in Postmenopausal Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med 2012; 366: 520-9.

3. Bachelot T, Bourgier C, Cropet C, et al. Randomized Phase II Trial of Everolimus in Combination with Tamoxifen in Patients with Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer with Prior Exposure to Aromatase Inhibitors: A GINECO Study. J Clin Oncol 2012; 30: 2718-2724.

4. NCCN Clinical Practice Guidelines in Oncology, Breast Cancer (version 3.2014). http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (Accessed on January 30, 2015).

March 2015
Updated versions may be found at www.pbm.va.gov or http://vaww.pbm.va.gov