



**Medication Policy Manual**

**Policy No:** dru178

**Topic:** Afinitor®, Afinitor® Disperz, everolimus

**Date of Origin:** May 8, 2009

**Committee Approval Date:** November 11, 2016

**Next Review Date:** November 2017

**Effective Date:** December 1, 2016

### **IMPORTANT REMINDER**

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

### **Description**

Everolimus (Afinitor) is an oral medication used to treat certain types of cancer and other non-malignant tumors. It works by blocking several tyrosine kinases which may temporarily slow the growth of tumors.

## Policy/Criteria

- I. Most contracts require prior authorization approval of everolimus (Afinitor) prior to coverage. Everolimus (Afinitor) may be considered medically necessary for any of the following conditions:
- A. Hormone receptor-positive, HER2-negative advanced (recurrent or progressive) breast cancer when criteria 1 and 2 below are met:
    - 1. Prior treatment with anastrozole or letrozole was not effective.

**AND**

    - 2. Everolimus (Afinitor) is given in combination with exemestane.
  - OR**

B. Renal angiomyolipoma and tuberous sclerosis complex.
  - OR**

C. Pancreatic neuroendocrine tumor (PNET) when prior therapy with sunitinib (Sutent) has been ineffective, is contraindicated, or was not tolerated.
  - OR**

D. Renal cell carcinoma (RCC) when prior therapy with sunitinib (Sutent) has been ineffective, is contraindicated, or was not tolerated.
  - OR**

E. Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis when criteria 1 and 2 below are met:
    - 1. Surgical resection is not an option.

**AND**

    - 2. The condition is associated with functional impairment (e.g. seizures, motor abnormalities, pain).
  - OR**

F. Waldenström's macroglobulinemia.
- II. Administration, Quantity Limitations, and Authorization Period
- A. OmedaRx considers everolimus (Afinitor) to be a self-administered medication.
  - B. When prior authorization is approved, up to 30 everolimus (Afinitor) tablets may be authorized per month. When everolimus (Afinitor) is administered concomitantly with medications that **decrease** its serum concentrations (See *Appendix I*), the following additional quantities may be covered:
- |                                      |                                    |
|--------------------------------------|------------------------------------|
| Afinitor 7.5 mg or 10 mg             | Up to 60 tablets per month         |
| Afinitor Disperz 2 mg, 3 mg, or 5 mg | Up to 60 soluble tablets per month |
- C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.
- III. Everolimus (Afinitor) is considered investigational when given concomitantly with any other cytotoxic or targeted chemotherapy medication.

- IV. Everolimus (Afinitor) is considered investigational when used for all other conditions, including but not limited to:
- A. Prevention of allograft rejection after solid organ transplant (e.g. lung, kidney, heart)
  - B. HER2-positive breast cancer
  - C. Colorectal cancer (CRC)
  - D. Crohn's disease
  - E. Functional (associated with symptoms of hormonal hypersecretion) carcinoid tumors
  - F. Gastric cancer
  - G. Gastrointestinal stromal tumor (GIST)
  - H. Glioblastoma
  - I. Hepatocellular carcinoma (HCC)
  - J. Metastatic melanoma
  - K. Neuroendocrine tumors (NET) of gastrointestinal or lung origin
  - L. Thymic carcinoma
  - M. Thymoma

#### Position Statement

- Everolimus (Afinitor), an orally administered inhibitor of mTOR, has been shown to be safe and effective in several cancer-related and non-cancer-related conditions.
- Everolimus (Afinitor) has been FDA approved for and may be an option for the treatment of some women with hormone receptor-positive, HER2-negative invasive breast cancer; however, its clinical benefit is unclear because although a small improvement in median PFS was reported in this population, no improvement in any clinically relevant outcomes such as OS has been demonstrated.
- Everolimus (Afinitor) has also been evaluated in and is FDA approved for two rare non-cancer conditions for which there are few established treatment options:
  - \* Renal angioliopoma and tuberous sclerosis complex.
  - \* Subependymal giant cell astrocytoma associated with tuberous sclerosis when surgical resection is not an option.
- Everolimus (Afinitor) may be an option in advanced renal cell carcinoma (RCC) when disease has progressed during or following treatment with a tyrosine kinase inhibitor (TKI), or in the treatment of advanced pancreatic neuroendocrine tumor (pNET).
  - \* As there is no useful evidence supporting superior effectiveness of one TKI over another in the first-line advanced RCC treatment setting, when a TKI is indicated, sunitinib (Sutent) provides the best overall value.
  - \* There is no useful evidence supporting superior effectiveness of everolimus (Afinitor) over sunitinib (Sutent), another medication approved for use in pNET. Among these two medications, sunitinib (Sutent) provides the best value.

- Everolimus (Afinitor) is also approved for unresectable or metastatic neuroendocrine tumor of gastrointestinal or lung origin. However, its use in this condition is considered investigational because it failed to improve overall survival (OS) or to provide any other clinical benefit in this population (relative to placebo). Furthermore, there is major disagreement among the NCCN neuroendocrine tumor panel as to whether this therapy should be recommended as an option for use in this population.
- Although the evidence of efficacy for everolimus (Afinitor) in Waldenström's macroglobulinemia is generally of poor quality, coverage is provided due to the lack of treatment options and overall poor quality of evidence for other interventions in this limited population.
- There is currently not sufficient evidence to support the safety and effectiveness of everolimus (Afinitor) in other types of cancer.
- The safety and effectiveness of concomitant administration of everolimus (Afinitor) and cytotoxic chemotherapy or other targeted therapies has not been adequately studied.
- The potential for slowing tumor growth with everolimus (Afinitor) must be weighed against the risk of adverse effects with this medication, which may be poorly tolerated.
- Everolimus (Afinitor) may be covered at the doses at which it has been shown to be effective. The usual dose is 5 to 10 mg orally once daily. Drug-drug interactions may necessitate dose adjustments.

### *Efficacy*

#### BREAST CANCER, HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE

- A large, phase III study (BOLERO-2) evaluated everolimus (Afinitor) plus exemestane versus exemestane alone in patients with hormone-receptor-positive, HER2-negative advanced breast cancer who had previous therapy with a non-steroidal aromatase inhibitor (anastrozole or letrozole). [1,2]
  - \* The trial reported a progression-free survival (PFS) advantage of approximately 4.5 months with everolimus (Afinitor) plus exemestane versus exemestane alone.
  - \* The modest improvement in median PFS (a surrogate endpoint) reported with the addition of everolimus (Afinitor) to exemestane did not ultimately translate to a clinically meaningful benefit in this population. In a final analysis, there was no difference in median overall survival (OS) between the exemestane plus everolimus (Afinitor) and exemestane alone treatment groups. [3]
- The current NCCN guideline recommends the use of everolimus (Afinitor) for HER2 negative, hormone-receptor positive breast cancer that has progressed within 12 months, was previously treated with a nonsteroidal aromatase inhibitor, or was treated with tamoxifen at any time (category 2A recommendation). [4]

#### RENAL ANGIOMYOLIPOMA WITH TUBEROUS SCLEROSIS COMPLEX

- Tuberous sclerosis complex is a genetic disorder that causes benign tumor growth throughout the body. Angiomyolipoma is the most common renal lesion observed among patients with tuberous sclerosis complex. [5]

- Although renal involvement is common in tuberous sclerosis complex, the majority of patients have few or no symptoms related to the renal disease. [5]
- Therapeutic interventions are required in a minority of patients with renal lesions associated with tuberous sclerosis complex. Potential interventions include nephron-sparing surgery, selective renal artery embolization, complete or radical nephrectomy, radiofrequency ablation, and mTOR inhibitors. [5]
- A low quality, randomized, double-blind, placebo-controlled trial evaluated the effects of everolimus (Afinitor) on tumor volume in patients with renal angiomyolipoma as a feature of tuberous sclerosis complex. [1]
  - \* Patients received everolimus (Afinitor) or placebo until disease progression or unacceptable toxicity.
  - \* Response rate was measured radiographically and included a 50% or greater reduction in angiomyolipoma volume, absence of new angiomyolipoma lesions  $\geq 1$  cm, absence of kidney volume increase  $\geq 20\%$ , and no angiomyolipoma related bleeding of grade 2 or greater.
  - \* The reported renal angiomyolipoma response rate was 42% in the everolimus (Afinitor) group and 0% in the placebo group.
- Long term clinical outcomes with everolimus (Afinitor) therapy in this population have not been evaluated.

#### PANCREATIC NEUROENDOCRINE TUMORS (pNET)

- There is a single, unreliable, randomized controlled trial comparing everolimus (Afinitor) 10 mg orally daily with placebo (best supportive care) in 410 patients with pNET. [6]
  - \* Patients enrolled in this study were diagnosed with low- or intermediate-grade, unresectable or metastatic pNET and who had disease progression within the prior 12 months.
  - \* Overall, the study was well designed (a large, randomized controlled trial with appropriate comparator); however, elements of bias cannot be ruled out for reasons that include lack of blinding and large differential loss (exceeding 5%) between treatment groups.
  - \* There was approximately a six-month improvement in median PFS with everolimus (Afinitor) versus placebo (11.4 months and 5.4 months, respectively). [19]
  - \* Adverse effects leading to discontinuation of therapy were reported in 17% versus 3% of patients receiving everolimus (Afinitor) and placebo, respectively.
  - \* Based on preliminary evidence, it appears that everolimus (Afinitor) may shrink tumors and delay the progression of this disease; however, it is not known whether it improves median OS in this population. Because the vast majority of patients (73%) that were randomized to placebo crossed over to everolimus (Afinitor) after progression of their disease, this study will not be able to accurately assess OS.
- The NCCN neuroendocrine tumors guideline lists everolimus (Afinitor) among several options for unresectable and/or metastatic pNET (category 2A recommendation). [7]

## NEUROENDOCRINE TUMORS (NET) OF GASTROINTESTINAL OR LUNG ORIGIN

- A placebo-controlled RCT evaluated the effects of everolimus (Afinitor) on disease progression (radiographic) in patients with progressive, advanced (unresectable or metastatic) neuroendocrine tumors of gastrointestinal or lung origin. [8]
  - \* Subjects included in the study were required to have tumors that were well-differentiated (Grade 1 or 2 based on 2010 WHO classification), and non-functional (not associated with symptoms of hormonal hypersecretion). Subjects with functional carcinoid tumors were excluded from the study.
  - \* Subjects had radiographic disease progression on prior therapy for their NET; however, no more than one prior line of cytotoxic chemotherapy was allowed. Those receiving prior therapy with an mTOR inhibitor were also excluded from the study.
  - \* A 7-month improvement in median PFS was demonstrated in the everolimus (Afinitor) treatment arm relative to the placebo arm (11.0 months versus 3.9 months; hazard ratio 0.48, 95% confidence interval of 0.35 to 0.67); however, there was no difference in median OS between the two groups, and no other clinical benefit has been demonstrated.
  - \* PFS is a surrogate endpoint that has not been shown to directly correlate with clinical benefit (e.g. improved OS, symptom control, quality of life) in NETs.
- There is major disagreement among the NCCN neuroendocrine tumors guideline panel as to whether everolimus (Afinitor) is appropriate for use in progressive, advanced NET of lung or gastrointestinal origin (category 3 recommendation). Other recommendations in this setting include octreotide or lanreotide (category 2A), hepatic regional therapy/ embolization or cytoreductive/ablative therapy (category 2B), or interferon alfa-2b or cytotoxic chemotherapy (category 3). [7]

## RENAL CELL CARCINOMA

- A single unreliable study compared everolimus (Afinitor) with placebo (best supportive care) in patients with advanced renal cell carcinoma. [1,9,10]
  - \* Patients enrolled in the trial had progression of their disease while on treatment with sorafenib (Nexavar) or sunitinib (Sutent) or both medications given sequentially.
  - \* PFS, a measure of tumor size using x-rays, was the primary endpoint of the study. PFS is not an accurate predictor of clinically relevant outcomes in RCC.
  - \* Everolimus (Afinitor) improved median PFS by a median of 3 months when compared with placebo. Its effect on median OS is uncertain due to the high rate of crossover that occurred during the study.
- A recent trial reported that concomitant use of lenvatinib (Lenvima) and everolimus (Afinitor) improved PFS relative to everolimus (Afinitor) alone when given to subjects with progressive advanced or metastatic RCC. [11] There is currently no evidence that this regimen improves any clinical outcome.
- The current NCCN kidney cancer guideline recommends everolimus (Afinitor) be given in combination with lenvatinib (Lenvima) for advanced RCC after progression with TKI therapy (category 1 recommendation, clear cell histology only). As a monotherapy, it received a lower recommendation (category 2A, both clear and non-clear histology). [12]

## SUBPENDYMAL GIANT CELL ASTROCYTOMA ASSOCIATED WITH TUBEROUS SCLEROSIS COMPLEX

- Tuberosus sclerosis complex is a genetic disorder that causes benign tumor growth throughout the body. Subependymal giant cell astrocytomas are characteristic brain tumors associated with tuberous sclerosis complex. [13]
- One double-blind, placebo-controlled trial evaluated everolimus (Afinitor) in 117 patients with subependymal giant cell astrocytoma associated with tuberous sclerosis complex. [14]
  - \* Patients in the everolimus (Afinitor) group had a least 50% reduction in the volume of astrocytomas versus no reduction in the placebo group (difference 35%; 95% CI: 15, 52;  $p < 0.0001$ ).
  - \* Decreased tumor volume has uncertain clinical relevance and has not been correlated to outcomes such as improved disease symptoms or survival.
- Surgical resection is the standard of care and is considered curative; however, not all patients are candidates for resection and to date everolimus (Afinitor) is the only medication treatment shown to inhibit the tumor growth in this condition. [13]

## WALDENSTRÖM'S MACROGLOBULINEMIA

- Waldenström's macroglobulinemia (WM) is a rare condition (approximately three per million per year) affecting the bone marrow and blood. The median age of diagnosis is 64 years of age. Treatment is indicated only in patients with symptomatic WM. [15]
- Patients with asymptomatic (smoldering) WM typically do not require treatment because they have overall survival rates approximating that of the normal population.
- There is no optimal treatment for WM. [15]
- A small poor quality, uncontrolled trial in 50 patients evaluated everolimus (Afinitor) in the treatment of relapsed or refractory WM. [16] The studies for other medications used in the management of WM are of similar poor quality.
- NCCN treatment guidelines for WM recommend everolimus (Afinitor) as one of several treatment regimens for salvage treatment of WM (Category 2A). [17]

## USE IN OTHER CONDITIONS

- **Allograft rejection:** Zortress® is a low strength everolimus product that is approved for prevention of allograft rejection after solid organ transplant (liver, lung, heart and kidney). [18] Afinitor, a higher strength everolimus product, is not approved for this use. [1]
- **HER2-positive breast cancer:** Everolimus (Afinitor) has not demonstrated any clinical benefit in women with HER2-positive metastatic breast cancer.
  - \* The addition of everolimus (Afinitor) to trastuzumab (Herceptin) plus paclitaxel did not improve clinical outcomes as a first-line therapy for women with HER2-positive advanced breast cancer (BOLERO-1 trial). [19]
  - \* The addition of everolimus (Afinitor) to trastuzumab (Herceptin) and vinorelbine in women with HER2-positive advanced breast cancer who had treatment with a prior taxane and had resistance to trastuzumab (Herceptin) resulted in increased toxicity and only a small improvement (~ 5 weeks) in median PFS as compared with placebo. It is unknown if everolimus (Afinitor) improves overall survival or any other clinically relevant outcome in this population (BOLERO-3 trial). [20]

- **Functional carcinoid tumors:** Everolimus has not been shown to have any clinical benefit when used in the treatment of functional carcinoid tumors (functional tumors cause hypersecretion of hormones resulting in associated symptoms). [1]
- Everolimus (Afinitor) is also being studied in several other types of cancer including: **colorectal cancer (CRC), gastric cancer, gastrointestinal stromal tumor (GIST), glioblastoma, and metastatic melanoma.** Additional evidence is necessary to establish clinical benefit in these conditions. [21-23]
- **Crohn's disease:** The use of everolimus (Afinitor) in Crohn's disease is not associated with any clinical benefit. [24]
- **Hepatocellular carcinoma (HCC):** Everolimus (Afinitor) failed to improve OS (versus placebo) in patients with advanced HCC whose disease progressed during or after receiving sorafenib (Nexavar). [25]
- **Thymoma and thymic carcinoma:** Results from a small, uncontrolled, preliminary study (Abstract) evaluating disease control rates in patients receiving everolimus (Afinitor) for previously treated thymoma and thymic carcinoma appear promising. [26] However, the single-arm study design and the unknown clinical relevance of this endpoint are not sufficient to allow for any conclusions with regard to the potential clinical benefit of this therapy. Larger, controlled trials are necessary.

**OmedaRx performs independent analyses of oncology medications. The OmedaRx analysis and coverage policy may differ from NCCN guidelines.**

*Safety [1]*

- Common (incidence  $\geq$  30%) adverse reactions with everolimus (Afinitor) include: stomatitis (mouth sores), infections, rash, edema, asthenia, fatigue, cough, abdominal pain, nausea, fever, headache, decreased appetite and diarrhea.
- Non-infectious pneumonitis may occur with everolimus (Afinitor).
- Elevations in lipids and blood glucose, and bone marrow suppression are also commonly reported.
- There is a high potential for clinically significant drug-drug interactions with everolimus (Afinitor).
  - \* Everolimus (Afinitor) may slow the metabolism of medications that are processed by the CYP3A4 and CYP2D6 enzyme pathways.
  - \* Inhibitors (e.g. aprepitant, ketoconazole, erythromycin, verapamil) and inducers (e.g. rifampin, dexamethasone) of CYP3A4 and PgP may increase or decrease everolimus (Afinitor) blood concentrations, respectively.

*Dosing [1]*

- The recommended dose of everolimus (Afinitor) in breast cancer, advanced pNET, advanced RCC, or renal angiomyolipoma with tuberous sclerosis complex is 10 mg orally daily until disease progression or unacceptable toxicity occurs. Dosing in subependymal giant cell astrocytoma is based on body surface area. Dose reductions (5 mg orally daily) or interruption of therapy may be used to manage severe and/or intolerable side effects or lab abnormalities (e.g. elevated liver enzymes).



- Pharmacokinetic studies suggest that an increased dose of everolimus (Afinitor) may be necessary when given concomitantly with CYP3A4 inducers. Avoiding concomitant use of these agents is preferred when possible.

<b>Appendix 1: Strong CYP3A4 Inducers (Reduce Everolimus Serum Concentrations)</b>	
carbamazepine (Tegretol <sup>®</sup> , Epitol <sup>®</sup> )	rifabutin (Mycobutin <sup>®</sup> )
efavirenz (Sustiva <sup>®</sup> )	rifapentine (Priftin <sup>®</sup> )
nevirapine (Viramune <sup>®</sup> )	rifampin (Rifadin <sup>®</sup> )
phenobarbital	St. John's Wort
phenytoin (Dilantin <sup>®</sup> )	

<b>Cross References</b>
Avastin <sup>®</sup> , bevacizumab, Medication Policy Manual, Policy No. dru215
Cabometyx <sup>™</sup> , cabozantinib, Medication Policy Manual, Policy No. dru290
Imbruvica <sup>®</sup> , ibrutinib, Medication Policy Manual, Policy No. dru326
Inlyta <sup>®</sup> , axitinib, Medication Policy Manual, Policy No. dru273
Lenvima <sup>®</sup> , lenvatinib, Medication Policy Manual, Policy No. dru398
Nexavar <sup>®</sup> , sorafenib, Medication Policy Manual, Policy No. dru134
Opdivo <sup>®</sup> , nivolumab, Medication Policy Manual, Policy No. dru390
Rituxan <sup>®</sup> , rituximab, Medication Policy Manual, Policy No. dru214
Sutent <sup>®</sup> , sunitinib, Medication Policy Manual, Policy No. dru128
Velcade <sup>®</sup> , bortezomib, Medication Policy Manual, Policy No. dru190
Votrient <sup>®</sup> , pazopanib, Medication Policy Manual, Policy No. dru199
Cycle Management Program, Medication Policy Manual, Policy No. dru404

Codes	Number	Description
HCPCS	J8999	Oral chemotherapeutic drug, not otherwise classified
ICD-10	D30.00	Angiomyolipoma of kidney
ICD-10	C50.011, C50.012, C50.019, C50.021, C50.022, C50.029, C50.111, C50.112, C50.119, C50.121, C50.122, C50.129, C50.211, C50.212, C50.219, C50.221, C50.222, C50.229, C50.311, C50.312, C50.319, C50.321, C50.322, C50.329, C50.411, C50.412, C50.419, C50.421, C50.422, C50.429, C50.511, C50.512, C50.519, C50.521, C50.522, C50.529, C50.611, C50.612, C50.619, C50.621, C50.622, C50.629, C50.811, C50.812, C50.819, C50.821, C50.822, C50.829, C50.911, C50.912, C50.919, C50.921, C50.922, C50.929, Z85.3	Malignant neoplasm of breast
ICD-10	C25.4, C7B.00 – C7B.04, E16.1, E16.3, E16.8, Z85.07, Z85.858	Malignant neoplasm of endocrine pancreas
ICD-10	C64.1, C64.2, C64.9, C65.1, C65.2, C65.9, Z85.528	Malignant neoplasm of kidney
ICD-10	D43.2, D43.4	Subependymal Giant Cell Astrocytoma
ICD-10	C83.00 – C83.09, C88.0, Z85.72, Z85.79	Waldenström's macroglobulinemia

## References

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#### Revision History

Revision Date	Revision Summary
11/11/2016	<ul style="list-style-type: none"> <li>• Added neuroendocrine tumors of gastrointestinal or lung origin, a new FDA indication for everolimus (Afinitor), as 'investigational'.</li> <li>• Updated the list of uses considered to be investigational.</li> </ul>