everolimus (Afinitor®, Afinitor Disperz®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO125

Description

Everolimus (Afinitor, Afinitor Disperz) is an orally administered mammalian target of rapamycin (mTOR) inhibitor to reduce cell proliferation, angiogenesis, and glucose uptake.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
everolimus (generic Afinitor)	2.5 mg tablet	Angiomyolipoma of the kidney, tuberous sclerosis syndrome; Breast cancer, advanced, HR+, HER2 -, in combination with exemestane after failure with letrozole or anastrozole; Neuroendocrine tumor, gastrointestinal, lung or pancreatic, unresectable locally advanced or metastatic; Renal cell carcinoma, advanced disease; Subependymal giant cell astrocytoma	28 tablets/28 days For subependymal giant cell astrocytoma: quantity associated with 4.5 mg/m^2 daily
	5 mg tablet		
	7.5 mg tablet		
everolimus (Afinitor)	2.5 mg tablet		
	5 mg tablet		
	7.5 mg tablet		
	10 mg tablet		
everolimus (Afinitor Disperz)	2 mg tablet	Partial seizure, adjunct, tuberous sclerosis syndrome; Subependymal giant cell astrocytoma	Quantity associated with 5 mg/m^2 daily for partial seizure, 4.5 mg/m^2 daily for subependymal giant cell astrocytoma.
	3 mg tablet		
	5 mg tablet		

Initial Evaluation

I. Everolimus (Afinitor, Afinitor Disperz) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **OR**
      1. Everolimus (Afinitor Disperz) is requested; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist, hematologist, or neurologist; **AND**
   C. **Not** used in combination with any other oncolytic medication unless outlined below (e.g., exemestane in breast cancer); **AND**
   D. A diagnosis of one of the following:
      1. **Angiomyolipoma of the kidney, associated with tuberous sclerosis; AND**
         i. The member does not require immediate surgery; **AND**
            a. The request is for everolimus (Afinitor) 10 mg; **OR**
            b. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**
            c. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg; **AND**
               i. The member has a contraindication to generic everolimus [Note: everolimus (Afinitor Disperz) is not FDA-approved in this setting]; **OR**
      2. **Breast cancer; AND**
         i. The member is a post-menopausal woman; **AND**
         ii. The member has advanced or metastatic disease (Stage III or IV); **AND**
         iii. Disease is confirmed as hormone receptor positive (HR+) and HER2-negative; **AND**
         iv. The member has failed a non-steroidal aromatase inhibitor [e.g., letrozole (Femara), anastrozole (Arimidex)]; **AND**
         v. Everolimus or everolimus (Afinitor) will be used in combination with exemestane (Aromasin); **AND**
            a. The request is for everolimus (Afinitor) 10 mg; **OR**
            b. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**
            c. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg; **AND**
               i. The member has a contraindication to generic everolimus [Note: everolimus (Afinitor Disperz) is not FDA-approved in this setting]; **OR**
      3. Neuroendocrine tumor; AND
         i. The disease is progressive; **AND**
            a. Is of pancreatic origin; **OR**

b. Is of gastrointestinal or lung origin and disease is well-differentiated, non-functional, unresectable and locally advanced, or metastatic; **AND**
    i. The request is for everolimus (Afinitor) 10 mg; **OR**
    ii. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**
    iii. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg; **AND**
        a. The member has a contraindication to generic everolimus [Note: everolimus (Afinitor Disperz) is not FDA-approved in this setting]; **OR**

4. Renal cell carcinoma; AND
i. The member has advanced or metastatic (Stage III or IV) disease; **AND**
ii. The member has tried and failed <u>one</u> anti-angiogenic therapy (e.g. pazopanib [Votrient], bevacizumab [Avastin], sunitinib [Sutent], axitinib [Inlyta]); **AND**
iii. Everolimus (Afinitor) will be used as monotherapy; **<u>OR</u>** in combination with lenvatinib (Lenvima); **AND**
    a. The request is for everolimus (Afinitor) 10 mg; **OR**
    b. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**
    c. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg; **AND**
        1. The member has a contraindication to generic everolimus [Note: everolimus (Afinitor Disperz) is not FDA-approved in this setting]; **OR**

5. Subependymal giant cell astrocytoma; AND
i. The request is for everolimus (Afinitor) 10 mg; **OR**
ii. The request is for everolimus (Afinitor Disperz); **OR**
iii. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**
iv. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg is requested; **AND**
    a. The member has a contraindication to generic everolimus; **OR**

6. Partial seizure, associated with tuberous sclerosis syndrome; AND
i. The member is refractory to at least <u>two</u> other antiepileptic therapies (e.g., carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine); **AND**
ii. The member will continue therapy with at least <u>one</u> other antiepileptic medication (e.g., carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine); **AND**

iii. Everolimus (Afinitor Disperz) is requested [Note: everolimus (Afinitor) is not FDA-approved in this setting]

II. Everolimus (Afinitor) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Carcinoid tumor

III. Everolimus (Afinitor, Afinitor Disperz) is considered investigational when used for all other conditions, including but not limited to:
   A. Graft-versus-host disease
   B. Ependymoma
   C. Hodgkin Lymphoma or Non-Hodgkin Lymphoma
   D. Central nervous system cancers
   E. Kaposi's sarcoma
   F. Thymoma and thymic carcinoma
   G. Endometrial, ovarian, uterine cancers
   H. Prostate cancer
   I. Gastroesophageal carcinomas
   J. Waldenstrom macroglobulinemia

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Everolimus (Afinitor, Afinitor Disperz) is prescribed by, or in consultation with, an oncologist, hematologist, or neurologist; **AND**
IV. Member has exhibited a positive response to therapy, such as improvement or stability in disease or symptoms; **AND**
V. **Not** used in combination with any other oncolytic medication unless outlined below (e.g., exemestane in breast cancer); **AND**
VI. A diagnosis of one of the following:
   - **Angiomyolipoma of the kidney, associated with tuberous sclerosis; AND**
      i. The request is for everolimus (Afinitor) 10 mg; **OR**
      ii. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**
      iii. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg; **AND**

1. The member has a contraindication to generic everolimus [Note: everolimus (Afinitor Disperz) is not FDA-approved in this setting]; **OR**

- **Breast cancer; AND**
  i. Everolimus (Afinitor) will be used in combination with exemestane (Aromasin); **AND**
  ii. The request is for everolimus (Afinitor) 10 mg; **OR**
  iii. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**
  iv. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg; **AND**
    1. The member has a contraindication to generic everolimus [Note: everolimus (Afinitor Disperz) is not FDA-approved in this setting]; **OR**
- **Neuroendocrine tumor; AND**
  i. The request is for everolimus (Afinitor) 10 mg; **OR**
  ii. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**
  iii. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg; **AND**
    1. The member has a contraindication to generic everolimus [Note: everolimus (Afinitor Disperz) is not FDA-approved in this setting]; **OR**
- **Renal cell carcinoma; AND**
  i. Everolimus (Afinitor) will be used as monotherapy; **OR** in combination with lenvatinib (Lenvima); **AND**
  ii. The request is for everolimus (Afinitor) 10 mg; **OR**
  iii. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**
  iv. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg; **AND**
    1. The member has a contraindication to generic everolimus [Note: everolimus (Afinitor Disperz) is not FDA-approved in this setting]; **OR**
- **Subependymal giant cell astrocytoma; AND**
  i. The request is for everolimus (Afinitor) 10 mg; **OR**
  ii. The request is for everolimus (Afinitor Disperz); **OR**
  iii. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**
  iv. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mgd; **AND**
    1. The member has a contraindication to generic everolimus; **OR**
- **Partial seizure, tuberous sclerosis syndrome associated; AND**
  i. The member will continue therapy with at least one other antiepileptic medication (e.g., carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine); **AND**
  ii. Everolimus (Afinitor Disperz) is requested [Note: everolimus (Afinitor) is not FDA-approved in this setting]

Supporting Evidence

I. Everolimus (Afinitor, Afinitor Disperz) has been evaluated in many clinical studies for various indications; however, they were focused on oncological indications (and not for transplantation management and rejection prophylaxis). Of note, everolimus (Zortress) does not have a prior authorization and is indicated for transplantation management and rejection prophylaxis. Everolimus products (Afinitor, Afinitor Disperz, Zortress) are not interchangeable, and it is recommended that utilization stay within the products' FDA-approved indication(s). Given the much lower cost as well as timely need for transplant medication access, prior authorization for everolimus (Zortress) is not commonly utilized.

II. Everolimus (Afinitor Disperz) received FDA-approval for subependymal giant cell astrocytoma related to tuberous sclerosis complex (TSC), and TSC associated partial onset seizures for adult as well as pediatric patients. On the contrary, everolimus (Afinitor) has FDA-approval only for adult patients (18 years and older) for all approved indications.

III. Everolimus (Afinitor) has been evaluated in combination with exemestane for HR+, HER2-, advanced or metastatic breast cancer. In clinical trials, subjects had previously progressed on or after an aromatase inhibitor, such as, anastrozole or letrozole. Additionally, subjects may have received one or more previous lines of chemotherapy. The major efficacy outcome was progression-free survival (PFS) which was statistically significant versus placebo; however, an overall survival (OS) benefit was not shown.

IV. Everolimus (Afinitor) was evaluated for safety and efficacy in neuroendocrine tumors, including those of pancreatic, lung, and gastrointestinal origin. Subjects were allowed previous somatostatin analog use, and the major efficacy outcome, PFS, was statistically significant regardless of previous somatostatin use in comparison to placebo. Overall survival was not statistically different between the treatment arms.

V. Everolimus (Afinitor) has been evaluated for safety and efficacy in renal cell carcinoma in patients who have previously received sunitinib (Sutent), sorafenib (Nexavar), or both sequentially. Subjects may also have had bevacizumab (Avastin), interleukin 2, or interferon alpha. Progression-free survival was shown to be statistically significant in favor of everolimus (Afinitor); however, OS was not statistically different compared to placebo. Results may have been confounded by high rates of crossover from placebo to active therapy (80%).

VI. A phase two, randomized trial to study efficacy and safety of lenvatinib (Lenvima) in renal cell carcinoma included everolimus (Afinitor) as active comparator. Lenvatinib (Lenvima) was administered in combination with everolimus (Afinitor) to the participants in treatment arm. Subjects in treatment arm had progressed on previous anti-angiogenesis therapy (VEGF-targeted therapy) such as pazopanib [Votrient], bevacizumab [Avastin], sunitinib [Sutent], or axitinib [Inlyta]. Primary outcome of progression-free survival (PFS) was shown to be statistically significant in favor of combination of lenvatinib (Lenvima) with everolimus (Afinitor) as compared to everolimus (Afinitor) monotherapy comparator. NCCN guidelines recommend

everolimus (Afinitor) in combination with lenvatinib (Lenvima) and everolimus (Afinitor) monotherapy as category 1 and category 2A recommendations, respectively.

VII. Everolimus (Afinitor) was evaluated for safety and efficacy in tuberous sclerosis complex associated renal angiomyolipomas. Response rate was statistically significant in favor of everolimus (Afinitor), as well as the time to progression compared to placebo.

VIII. Everolimus (Afinitor, Afinitor Disperz) was evaluated in tuberous sclerosis completed-associated subependymal giant cell astrocytomas. Subjects included were of pediatric and adult populations. The primary outcome was SEGA response rate, which was statistically significant in favor of everolimus (Afinitor, Afinitor Disperz).

IX. Everolimus (Afinitor Disperz) was evaluated as an adjunct therapy for partial onset seizures associate with tuberous sclerosis complex (TSC). Subjects included were refractory to at least two conventional antiepileptic medications.

X. Everolimus is the AB-rated generic of everolimus (Afinitor) and as of October 2020, the 2.5 mg, 5 mg, and 7.5 mg strengths have generic availability. Medical necessity for brand Afinitor will be indicated by a contraindication to generic as intolerance to the generic is an indicator of intolerance to brand, given their therapeutic equivalence. Everolimus (Afinitor Disperz) is only available as brand (2 mg, 3 mg, and 5 mg).

Investigational or Not Medically Necessary Uses

I. Carcinoid tumor
   A. Everolimus (Afinitor) was evaluated in a clinical trial for safety and efficacy for carcinoid tumor. The primary efficacy outcome was not reached, and overall survival outcomes favored placebo. At this time efficacy of everolimus (Afinitor) in this setting is not known to be clinically beneficial.

II. Everolimus (Afinitor, Afintor Disperz) has not been sufficiently evaluated for safety and/or efficacy, and/or is in clinical trials for the following indications:
   A. Graft-versus-host disease
   B. Ependymoma
   C. Hodgkin Lymphoma or Non-Hodgkin Lymphoma
   D. Central nervous system cancers
   E. Kaposi's sarcoma
   F. Thymoma and thymic carcinoma
   G. Endometrial, ovarian, uterine cancers
   H. Prostate cancer
   I. Gastroesophageal carcinomas
   J. Waldenstrom macroglbulinemia

References

1. Afinitor, Afinitor Disperz [Prescribing Information]. Novartis Pharmaceuticals Corporation. East Hanover, NJ. April 2018.
2. Baselga, K., Campone M., Piccart M., et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med.* 2012: 366(6): 520-529.
3. French JA., Lawson JA, Yapici Z., et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associagted with tuberous sclerosis: a Phase 3, randomized, double-blind, placebo-controlled study. *Lancet*. 2016: 388(10056):2153-2163.
4. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet*. 2008;372(9637):449-56.
5. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2016;387(10022):968-977.
6. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med.* 2011;364(6):514-23.
7. Franz DN, Belousova E, Sparagana S, et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet*. 2013;381(9861):125-32.
8. Motzer RJ, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol. 2015 Nov;16(15):1473-1482.
9. U.S. Food&Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available at: https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Accessed December 30, 2019.
10. NCCN guidelines for kidney cancer, version 01.2021; 07/15/2020. Accessed 10/08/2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy for renal cell carcinoma to allow after trial and failure of one prior anti-angiogenic therapy rather than only sorafenib (Nexavar) or sunitinib (Sutent); and combination of everolimus (Afinitor) with lenvatinib (Lenvima); Updated supporting evidence to include clinical data; Added supporting evidence for FDA-approvals based on age for everolimus (Afinitor) and everolimus (Afinitor Disperz)	10/2020
Generic everolimus 2.5 mg, 5 mg, and 7.5 mg added to the policy, with brand coverage only if medical necessity established for brand over generic.	01/2020
Prior authorization criteria transitioned to policy format, specialist providers updated to include neurologist, Addition of trial of conventional antiepileptic therapies prior to payment consideration for everolimus (Afinitor Disperz), addition of age requirement for everolimus (Afinitor), updated QLL for everolimus (Afinitor Disperz) to be calculated upon clinical review.	12/2019
Afinitor Disperz with indications added to criteria, formatting update and quantity limits changed to mirror available package sizes.	05/2018
Criteria created	05/2012