09-J1000-45

Original Effective Date: 01/01/12

Reviewed: 01/08/20

Revised: 02/15/20

Subject: Everolimus (Afinitor®, Afinitor Disperz®) Tablets

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Everolimus is currently marketed under three proprietary names: Afinitor®, Afinitor Disperz®, and Zortress®. Afinitor and Afinitor Disperz are antineoplastic agents that exert their activity through inhibition of mammalian target of rapamycin (mTOR). The mTOR pathway is dysregulated in many human cancers and inhibition of the pathway has been shown to reduce cell proliferation, angiogenesis, and glucose uptake by the tumor. The Food and Drug Administration (FDA) has approved everolimus (Afinitor) for the treatment of breast cancer, various types of neuroendocrine tumors, advanced renal cell carcinoma, renal angiomyolipoma and tuberous sclerosis complex (TSC), and TSC with subependymal giant cell astrocytoma (SEGA). In addition to FDA approved indications, the National Comprehensive Cancer Network (NCCN) Guidelines recommend use of everolimus for the treatment of endometrial carcinoma, Hodgkin lymphoma, and various types of soft tissue sarcomas. The FDA has approved everolimus tablets for oral suspension (Afinitor Disperz) for TSC with SEGA and as adjunctive treatment for TSC associated partial-onset seizures.

Zortress is a macrolide immunosuppressant and is structurally related to sirolimus. It is indicated for kidney and liver transplant prophylaxis. The contents of this medical coverage guideline apply only to the use of Afinitor and Afinitor Disperz.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

I. Initiation of everolimus (Afinitor, Afinitor Disperz) **meets the definition of medical necessity** when **ALL** of the following are met:

   a. Everolimus (Afinitor, Afinitor Disperz) is used to treat an indication listed in Table 1 and all of the indication specific criteria are met for the requested formulation

   b. The dose does not exceed 10 mg daily* using the fewest number of tablets per day

   c. For brand Afinitor only, the member has tried and had intolerable adverse effects to generic everolimus (if a generic formulation of everolimus is available in the strength requested) and **ALL** of the following must be submitted:

      i. The specific intolerance(s) and rationale for using brand Afinitor must be specified

      ii. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda

      iii. Completed Naranjo Adverse Drug reaction probablility scale - https://livertox.nih.gov/Naranjoassessment.pdf

Table 1

Indication	Specific Criteria
Everolimus (Afinitor)	
Breast cancer	Member has recurrent or metastatic, hormone receptor positive (HR+)/ human epidermal growth factor receptor type 2 (HER2)-negative breast cancer and **BOTH** of the following: 1. **ONE** of the following: a. Everolimus will be used in combination with exemestane (Aromasin) and member's prior endocrine therapy included a nonsteroidal aromatase inhibitor (e.g., letrozole [Femara] or anastrozole [Arimidex]) or tamoxifen b. Everolimus will be used in combination with fulvestrant (Faslodex) or tamoxifen 2. **ONE** of the following: a. Member is postmenopausal b. Member is premenopausal and treated with ovarian ablation/suppression c. Member is a biological male

CNS Cancer	When used for adult low-grade (WHO grade II) infiltrative supratentorial astrocytoma/oligodendroglioma as adjuvant treatment for subependymal giant cell astrocytoma (SEGA) as a single agent
Endometrial carcinoma	When used in combination with letrozole for recurrent, metastatic, or high-risk disease with endometrioid histology
Hodgkin Lymphoma	When used as a single agent for relapsed or refractory disease
Kidney Cancer	**ALL** of the following: 1. Member has relapsed or stage IV disease 2. **ONE** of the following: a. When used as subsequent therapy for disease with predominant clear cell histology as a single agent or in combination with lenvatinib* (Lenvima) b. When used for treatment of disease with non-clear cell histology as a single agent or in combination with **ONE** of the following: i. lenvatinib* ii. bevacizumab (Avastin)
Neuroendocrine tumor of the Gastrointestinal (GI) tract, Lung, or Thymus	When used for **ONE** of the following: 1. Unresectable 2. Locoregional advanced disease 3. Metastatic disease
Pancreatic neuroendocrine tumor (pNET)	When used as a single agent in member's with unresectable disease, locoregional advanced disease, or distant metastatic disease and **ONE** of the following: 1. Progressive disease 2. Symptomatic disease 3. Significant tumor burden
Renal angiomyolipoma with tuberous sclerosis complex (TSC)	Member's disease does not require immediate surgery
Soft-tissue sarcoma (STS)	When used for **ONE** of the following: 1. Perivascular epithelioid cell tumor(s) (PEComa) when used as a single agent 2. Recurrent angiomyolipoma when used as a single agent

	3. Lymphangioleiomyomatosis when used as a single agent 4. Gastrointestinal Stromal Tumor for disease progression after single-agent therapy with imatinib, sunitinib, and regorafenib and will be used in combination with **ONE** of the following: a. imatinib (Gleevec) b. sunitinib (Sutent) c. regorafenib (Stivarga)
Subependymal giant cell astrocytoma (SEGA) with tuberous sclerosis complex (TSC)*	Member cannot be curatively resected
Thymomas or Thymic carcinoma	When used as a single agent as second-line therapy
Thyroid cancer; Follicular carcinoma Hurthle cell carcinoma Papillary carcinoma	When used as a single agent for iodine-refractory symptomatic or progressive disease classified as **ONE** of the following: 1. Unresectable locoregional disease that is recurrent or persistent 2. Distant metastatic disease
Waldenström's macroglobulinemia / lymphoplasmacytic lymphoma	When used as a single agent for **ONE** of the following: 1. Relapsed disease 2. Progressive disease 3. For previously treated disease unresponsive to primary therapy
Other FDA-approved or NCCN supported diagnosis (not previously listed above)	**ONE** of the following is met: 1. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert) 2. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation
Afinitor Disperz	
Subependymal giant cell astrocytoma with tuberous sclerosis complex*	Member cannot be curatively resected
Tuberous sclerosis complex* associated partial-onset	When used in combination with an antiepileptic

seizures	
Other FDA-approved or NCCN supported diagnosis (not previously listed above)	**ONE** of the following is met: 1. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert) 2. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation
HR+, hormone-receptor positive; HER2, human epidermal growth factor receptor type 2; NET, neuroendocrine tumor; PNET, pancreatic neuroendocrine tumor; RCC, renal cell carcinoma; SEGA, subependymal giant cell astrocytoma; STS, soft-tissue sarcoma; TSC, tuberous sclerosis complex	

Approval duration: 6 months (all indications)

II. Continuation of everolimus (Afinitor®, Afinitor Disperz®,) **meets the definition of medical necessity** for the indications in Table 1 above when the following criteria are met:

A. The member's disease has not progressed while receiving treatment with everolimus

B. The member has been previously approved by Florida Blue or another health plan in the past 2 years, OR the member has previously met all indication-specific criteria for coverage

C. The dose does not exceed 10 mg once daily* and will be provided using the fewest number of tablets per day

D. For brand Afinitor only, the member has tried and had intolerable adverse effects to generic everolimus (if a generic formulation of everolimus is available in the strength requested) and **ALL** of the following must be submitted†:

1. The specific intolerance(s) and rationale for using brand Afinitor must be specified
2. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda
3. Completed Naranjo Adverse Drug reaction probablility scale - https://livertox.nih.gov/Naranjoassessment.pdf

Approval duration: 1 year

***NOTE:** A maximum dose of 5 mg once daily is permitted when use is in combination with lenvatinib for kidney cancer. A dose greater than 10 mg daily will be permitted for FDA-approved indications. Per FDA-labeling, subependymal giant cell astrocytoma (SEGA) with tuberous sclerosis complex (TSC) dosing is 4.5 mg/m2 once daily and may be modified to attain trough concentrations of 5-15 ng/mL. TSC associated partial-onset seizure dosing is 5 mg/m2 once daily and may be modified to attain trough concentrations of 5-15 ng/mL. Avoid use with strong CYP3A4/P-glycoprotein inhibitors and inducers. If CYP3A4/P-glycoprotein strong inducers (e.g. phenytoin, carbamazepine, rifampin, rifabutin, rifapentine,

phenobarbital) cannot be avoided, the dose may need to be increased to 9 mg/m2 and modified using therapeutic drug monitoring when used for SEGA with TSC. If CYP3A4/P-glycoprotein strong inducers cannot be avoided for other indications (breast cancer, pNET, RCC, renal angiomyolipoma with TSC), the dose may need to be increased using increments of 5 mg or less. A dose reduction should be considered for all labeled indications if coadministration with CYP3A4/P-glycoprotein inhibitors cannot be avoided.

†Step therapy requirement does not apply if a prior health plan paid for the medication - documentation of a paid claim within the past 90 days must be submitted

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

Afinitor FDA-approved indications:

- Treatment of advanced breast cancer in postmenopausal women when the disease is hormone-receptor positive, HER2-negative, the individual has failed letrozole or anastrozole and everolimus will be used in combination with exemestane.
- Adults with progressive neuroendocrine tumors of pancreatic origin (PNET) and adults with progressive, well-differentiated, non-functional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin that are unresectable, locally advanced or metastatic
- Adults with advanced renal cell carcinoma (RCC) following sunitinib or sorafenib failure
- Adults with renal angiomyolipoma and tuberous sclerosis complex (TSC) not requiring immediate surgery
- Pediatrics and adults with TSC who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.

Afinitor Disperz FDA-approved indications:

- Pediatrics and adults with TSC who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.
- Adjunctive therapy for pediatric and adult patients with TSC-associated partial-onset seizures.

Dosage

<table>
<tr><th colspan="2">FDA-approved dosage</th></tr>
<tr><td>Indication</td><td>Recommended dose</td></tr>
<tr><td>Advanced HR+/HER2- Breast cancer</td><td rowspan="4">10 mg once daily with or without food</td></tr>
<tr><td>Advanced PNET/NET</td></tr>
<tr><td>Advanced RCC</td></tr>
<tr><td>Renal angiomyolipoma with TSC</td></tr>
<tr><td>SEGA with TSC</td><td>4.5 mg/m2 once daily; adjust to attain trough concentrations of 5-15 ng/mL</td></tr>
<tr><td>TSC-associated partial-onset seizures</td><td>5 mg/m2 once daily; adjust to attain trough concentrations of 5-15 ng/mL</td></tr>
<tr><td colspan="2">HR+, hormone-receptor positive; HER2, human epidermal growth factor receptor type 2; PNET, pancreatic neuroendocrine tumor; RCC, renal cell carcinoma; TSC, tuberous sclerosis complex; SEGA, subependymal</td></tr>
</table>

giant cell astrocytoma.

Continue treatment until disease progression or unacceptable toxicity occurs.

Dose adjustments

Adverse reactions: Severe or intolerable adverse reactions may require temporary dose interruption (with or without a dose reduction) or discontinuation. If dose reduction is required, administering half of the original daily dose is recommended. See prescribing information for dose adjustment of specific adverse reactions.

Hepatic impairment: The initial dose should be reduced for hepatic impairment. For mild impairment (Child-Pugh class A) initiate at 7.5 mg and decrease to 5 mg if not well tolerated. For moderate hepatic impairment (Child-Pugh class B), initiate at 5 mg daily and decrease to 2.5 mg if not well tolerated. For severe hepatic impairment (Child-Pugh class C), if the benefit outweighs the risk of treatment, a maximum of 2.5 mg daily is recommended. For TSC patients with SEGA or patients with TSC-associated partial-onset seizures who have severe hepatic impairment, the starting dose should be reduced by 50%.

Drug Interactions: Avoid use with strong CYP3A4/P-glycoprotein inhibitors and inducers. See prescribing information for dose adjustments if co-administration cannot be avoided.

Food Interactions: Avoid use with foods or nutritional supplements known to inhibit or induce CYP3A4/P-glycoprotein.

Drug Availability

- Afinitor: supplied as a 2.5-, 5-, 7.5-, and 10 mg tablet
- Afinitor Disperz: supplied as 2-, 3-, and 5 mg tablets for oral suspension.

PRECAUTIONS:

Contraindication:

Everolimus in contraindicated in persons with a hypersensitivity to everolimus, to other rapamycin derivatives, or to any of the excipients contained in the formulation.

Warnings/Precautions:

- Non-infectious pneumonitis: Monitor for clinical symptoms or radiological changes; fatal cases have occurred. Manage by dose reduction or discontinuation until symptoms resolve, and consider use of corticosteroids
- Infections: Increased risk of infections, some fatal. Monitor for signs and symptoms, and treat promptly
- Severe hypersensitivity reactions: permanently discontinue for clinically significant hypersensitivity.
- Angioedema: Patients taking concomitant ACE inhibitor therapy may be at increased risk
- Oral ulceration: Mouth ulcers, stomatitis, and oral mucositis are common. Management includes mouthwashes and topical treatments
- Renal failure: Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed

- Impaired wound healing: Use caution and monitor signs and symptoms in the peri-surgical period due to increased risk of wound-related complications.
- Geriatric patients: Monitor and adjust dose for adverse reactions.
- Laboratory test alterations: Elevations of serum creatinine, urinary protein, blood glucose, and lipids may occur. Decreases in hemoglobin, neutrophils, and platelets may also occur. Monitor renal function, blood glucose, lipids, and hematologic parameters prior to treatment and periodically thereafter
- Metabolic disorders: Monitor serum glucose and lipids prior to treatment and periodically thereafter. Withhold or permanently discontinue based on severity.
- Myelosuppression: monitor hematologic parameters prior to treatment and periodically thereafter. Withhold or permanently discontinue based on severity.
- Vaccinations: Avoid live vaccines and close contact with those who have received live vaccines
- Embryo-fetal toxicity: Fetal harm can occur when administered to a pregnant woman. Advise women of potential harm to the fetus

BILLING/CODING INFORMATION:

HCPCS Coding

C9399	Unclassified drugs or biologicals
J8999	Prescription drug, oral, chemotherapeutic, NOS

ICD-10 Diagnosis Codes That Support Medical Necessity:

C25.4	Malignant neoplasm of endocrine pancreas
C37	Malignant neoplasm of thymus
C47.8	Malignant neoplasm of overlapping sites of peripheral nerves and autonomic nervous system
C49.00 – C49.9	Malignant neoplasm of other connective and soft tissue
C49.A0 – C49.A9	Gastrointestinal stromal tumor
C50.011 – C50.929	Malignant neoplasm of breast
C54.0 – C54.9	Malignant neoplasm of corpus uteri
C55	Malignant neoplasm of uterus, part unspecified
C64.1 – C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
C65.1 – C65.9	Malignant neoplasm of unspecified renal pelvis
C71.0 – C71.9	Malignant neoplasm of brain
C72.9	Malignant neoplasm of central nervous system, unspecified
C73	Malignant neoplasm of thyroid gland
C7A.00 – C7A.8	Malignant neuroendocrine tumors
C7B.00 – C7B.09	Secondary neuroendocrine carcinoid tumors
C7B.8	Other secondary neuroendocrine carcinoid tumors
C81.10 – C81.19	Nodular sclerosis classical Hodgkin Lymphoma
C81.20 – C81.29	Mixed cellularity classical Hodgkin Lymphoma
C81.30 – C81.39	Lymphocyte depleted classical Hodgkin Lymphoma
C81.40 – C81.49	Lymphocyte rich classical Hodgkin Lymphoma
C81.70 – C81.79	Other classical Hodgkin lymphoma
C81.90 – C81.99	Hodgkin Lymphoma unspecified

C83.00 – C83.09	Small cell B-cell lymphoma
C83.80 – C83.89	Other non-follicular lymphoma
C88.0	Waldenstrom macroglobulinemia
D15.0	Benign neoplasm of thymus
D43.0 – D43.2	Neoplasm of uncertain behavior of brain, unspecified
D43.4	Neoplasm of uncertain behavior of spinal cord
D49.2	Neoplasm of unspecified behavior of bone, soft tissue, and skin
E16.1	Hypoglycemia, other
E16.3	Increased secretion of glucagon
E16.8	Other specified disorders of pancreatic internal secretion
E34.0	Carcinoid syndrome

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT.**

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

Medicare Advantage: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline

DEFINITIONS:

Table 2: Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

RELATED GUIDELINES:

Erythropoiesis Stimulating Agents, 09-J0000-31

Gemcitabine (Gemzar®), 09-J0000-96

Radiofrequency Ablation of Solid Tumors Other Than Liver Tumors, 02-99221-13

OTHER:

TABLE 3: Stages of Renal Cell Cancer

Stage I	The tumor is 7 centimeters or smaller and is found only in the kidney.
Stage II	The tumor is larger than 7 centimeters and is found only in the kidney.
Stage III	The tumor is any size and cancer is found only in the kidney and in 1 or more nearby lymph nodes; or cancer is found in the main blood vessels of the kidney or in the layer of fatty tissue around the kidney. Cancer may be found in 1 or more nearby lymph nodes.
Stage IV	Cancer has spread beyond the layer of fatty tissue around the kidney and may be found in the adrenal gland above the kidney with cancer, or in nearby lymph nodes; or to other organs, such as the lungs, liver, bones, or brain, and may have spread to lymph nodes.

TABLE 4: Child-Pugh Score and Classification

	1 point	2 points	3 points
Total bilirubin	< 2	2-3	> 3
Serum albumin	> 3.5	2.8-3.5	< 2.8
INR	> 1.7	1.71-2.20	< 2.20
Ascites	None	Mild	Severe
Hepatic encephalopathy	None	Grade I-II	Grade III-IV
Classification of Result: Class A: 5-6 points Class B: 7-9 points Class C: 10-15 points			

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 01/08/20.

GUIDELINE UPDATE INFORMATION:

01/01/12	New Medical Coverage Guideline.
07/15/12	Revision to guideline; consisting of updating position statement, precautions, coding and references.
11/15/12	Review and revision to guideline; consisting of reformatting position statement and adding new indication, add contraindication, update coding, program exceptions and references.
01/01/13	Revision to guideline; consisting of updating codes.
12/15/13	Review and revision to guideline; consisting of revising positing statement, description, dosage/administration, and precautions section; updated references and program exceptions.
12/15/14	Review and revision to guideline; consisting of revising position statement and updating references.
12/15/15	Review and revision to guideline; consisting of revising position statement and updating dosage, precautions, coding and references.

07/15/16	Revision to guideline; consisting of updating position statement, dosing and references.
12/15/16	Review and revision to guideline; consisting of revising position statement, coding and updating references.
04/15/17	Revision to guideline; consisting of updating position statement, coding and references.
11/15/17	Review and revision to guideline; consisting of updating position statement and references.
01/15/18	Revision to guideline; consisting of updating position statement, coding and references.
01/15/19	Review and revision to guideline; consisting of updating position statement, description, dosing, coding and references.
06/15/19	Revision to guideline; consisting of updating position statement and references.
02/15/20	Review and revision to guideline; consisting of updating position statement and references.