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Section:	Prescription Drugs	**Effective Date:**	April 1, 2024
Subsection:	Antineoplastic Agents	**Original Policy Date:**	October 30, 2015
Subject:	Afinitor	**Page:**	1 of 10

Last Review Date: March 8, 2024

Afinitor

Description

Afinitor and Afinitor Disperz (**everolimus**)

Preferred product: generic everolimus

Background
Everolimus (Afinitor and Afinitor Disperz) is a macrolide immunosuppressant and a mechanistic target of rapamycin (mTOR) inhibitor which helps control cell division and reduce the growth of new blood vessels. The mTOR pathway is dysregulated in several human cancers and in tuberous sclerosis complex (TSC). Everolimus reduces protein creation and cell growth by binding to the FK binding protein-12 (FKBP-12), an intracellular protein, to form a complex that inhibits activation of mTOR (mechanistic target of rapamycin) serine-threonine kinase activity. Inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in in vitro and/or in vivo studies (1).

Regulatory Status
FDA-approved indications:
Afinitor is a kinase inhibitor that is indicated for: (2)

1. Postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole.
2. 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.

3. Adults with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib.
4. Adults with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery.

Afinitor Disperz is a kinase inhibitor indicated for: (2)

1. The treatment of adult and pediatric patients aged 2 years and older with TSC-associated partial-onset seizures.

Afinitor and Afinitor Disperz are kinase inhibitors indicated for the treatment of: (2)

1. Pediatric and adult patients with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.

Limitations of Use: (2)
Afinitor is not indicated for the treatment of patients with functional carcinoid tumors.

Off-Label Uses for Afinitor: (3,4)
Through randomized control trials and phase II studies, Afinitor has been found effective in the following disease states:

1. Lung neuroendocrine tumors
2. Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma
3. Soft Tissue sarcoma:
   a. Perivascular epithelioid cell tumors (PEComa)
   b. Recurrent angiomyolipoma
   c. Lymphangioleiomyomatosis
4. Classical Hodgkin lymphoma
5. Advanced HR-positive, HER2-negative breast cancer
   a. Used in combination with exemestane that progressed within 12 months, has been previously treated with a nonsteroidal aromatase inhibitor, or previously treated with tamoxifen
   b. Used in combination with an endocrine agent (e.g., exemestane, faslodex, or tamoxifen)
6. Gastrointestinal (GI) neuroendocrine tumors - metastatic or unresectable progressive disease
7. Thymus neuroendocrine tumors: metastatic or unresectable progressive disease
8. Osteosarcoma
9. Thymomas/Thymic carcinomas
10. Thyroid carcinoma: Papillary, Hürthle cell, and follicular thyroid carcinoma

11. Relapse or stage IV RCC:
    a. Systemic therapy for non-clear cell histology
    b. Subsequent therapy for predominant clear cell histology
12. Gastrointestinal stromal tumors (GIST): treatment in combination with either imatinib, sunitinib, or regorafenib for disease progression after single-agent therapy with imatinib, sunitinib, and regorafenib
13. Endometrial carcinoma: in combination with letrozole

Related policies

Fyarro

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Afinitor and Afinitor Disperz may be considered **medically necessary** if the conditions indicated below are met.

Afinitor and Afinitor Disperz may be considered **investigational** for all other indications.

Prior-Approval Requirements

Afinitor only

Age 18 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Renal Cell Carcinoma with **ONE** of the following:
    a. Disease is of non-clear cell histology
    b. Disease is of predominantly clear cell histology and has progressed on prior antiangiogenic therapy
2. Advanced HR-positive, HER2 negative breast cancer
    a. Patient has previously been treated with letrozole or anastrozole
    b. Used in combination with an endocrine agent (e.g., exemestane, fulvestrant, or tamoxifen)

3. Hodgkin's lymphoma
4. Lung neuroendocrine tumors
5. Soft tissue sarcoma that expresses **ONE** of the following histologies:
    a. PEComa/Recurrent
    b. Angiomyolipoma
    c. Lymphangioleiomyomatosis
6. Pancreatic neuroendocrine tumors
7. Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma
8. Renal angiomyolipoma with Tuberous Sclerosis Complex (TSC)
    a. Patient does **NOT** require immediate surgery
9. Gastrointestinal (GI) neuroendocrine tumors
    a. Metastatic or unresectable progressive disease
10. Thymus neuroendocrine tumors
    a. Metastatic or unresectable progressive disease
11. Osteosarcoma
    a. Patient has previously been treated with a first-line therapy agent
    b. Used in combination with sorafenib
12. Thymomas / Thymic carcinomas
13. Thyroid carcinoma that expresses **ONE** of the following histologies:
    a. Papillary
    b. Hürthle cell
    c. Follicular thyroid carcinoma
14. Gastrointestinal Stromal Tumors (GIST)
    a. Used in combination with either imatinib, sunitinib, or regorafenib
    b. Disease progression after single-agent therapy with imatinib, sunitinib, or regorafenib
15. Endometrial carcinoma
    a. Used in combination with letrozole

AND the following for **Brand Afinitor only:**

a. Patient **MUST** have tried the preferred product (generic Afinitor: everolimus) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

Afinitor Disperz only

Age 2 years of age or older

Diagnosis

Patient must have the following:

1. TSC associated partial-onset seizures.
    a. Used as adjunctive therapy
    b. **Brand Afinitor Disperz only:** Patient **MUST** have tried the preferred product (generic Afinitor Disperz: everolimus) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

Afinitor and Afinitor Disperz

Age 1 year of age or older

Diagnosis

Patient must have the following:

1. Subependymal Giant Cell Astrocytoma (SEGA) with TSC
    a. **NOT** a candidate for curative surgical resection
    b. **NOT** being used to prevent kidney transplant rejection
    c. **Brand Afinitor/Afinitor Disperz only:** Patient **MUST** have tried the preferred product (generic Afinitor/Afinitor Disperz: everolimus) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

Prior – Approval *Renewal* Requirements

Afinitor only

Age 18 years of age or older

Diagnoses

Patient must have **ONE** of the following

1. Renal cell carcinoma
2. Advanced HR-positive, HER2 negative breast cancer

   a. Used in combination with an endocrine agent (e.g., exemestane, fulvestrant, or tamoxifen)
3. Hodgkin's lymphoma
4. Lung neuroendocrine tumors
5. Soft tissue sarcoma that expresses **ONE** of the following histologies:
   a. PEComa/Recurrent
   b. Angiomyolipoma
   c. Lymphangioleiomyomatosis
6. Pancreatic neuroendocrine tumors
7. Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma
8. Renal Angiomyolipoma with Tuberous Sclerosis Complex (TSC)
9. Gastrointestinal (GI) neuroendocrine tumors
10. Thymus neuroendocrine tumors
11. Osteosarcoma
    a. Used in combination with sorafenib
12. Thymomas / Thymic carcinomas
13. Thyroid carcinoma that expresses **ONE** of the following histologies:
    a. Papillary
    b. Hürthle cell
    c. Follicular thyroid carcinoma
14. Gastrointestinal Stromal Tumors (GIST)
    a. Used in combination with either imatinib, sunitinib, or regorafenib
15. Endometrial carcinoma
    a. Used in combination with letrozole

AND the following for **Brand Afinitor only:**

   a. Patient **MUST** have tried the preferred product (generic Afinitor: everolimus) unless the patient has a valid medical exception (e.g., inadequate response, intolerance, contraindication)

Afinitor Disperz only

Age 2 years of age or older

Diagnosis

Patient must have the following:

1. TSC associated partial-onset seizures.
    a. Used as adjunctive therapy
    b. **Brand Afinitor Disperz only:** Patient **MUST** have tried the preferred product (generic Afinitor Disperz: everolimus) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

Afinitor and Afinitor Disperz

Age 1 year of age or older

Diagnosis

Patient must have the following:

1. Subependymal Giant Cell Astrocytoma (SEGA) with TSC
    a. **NOT** being used to prevent kidney transplant rejection
    b. **Brand Afinitor/Afinitor Disperz only:** Patient **MUST** have tried the preferred product (generic Afinitor/Afinitor Disperz: everolimus) unless the patient has a valid medical exception (e.g., inadequate response, intolerance, contraindication)

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity

Afinitor

Strength	Quantity
2.5 mg	180 tablets per 90 days **OR**
5 mg	180 tablets per 90 days **OR**
7.5 mg	90 tablets per 90 days **OR**
10 mg	90 tablets per 90 days

Maximum daily limit of any combination: 10 mg

OR

Afinitor Disperz

Strength	Quantity
2 mg	168 capsules per 84 days **OR**
3 mg	168 capsules per 84 days **OR**
5 mg	168 capsules per 84 days

Maximum daily limit of any combination: 10 mg

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Everolimus (Afinitor and Afinitor Disperz) is a macrolide immunosuppressant and a mechanistic target of rapamycin (mTOR) inhibitor which helps control cell division and reduce the growth of new blood vessels. The mTOR pathway is dysregulated in several human cancers and in tuberous sclerosis complex (TSC). Inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in in vitro and/or in vivo studies (1).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Afinitor and Afinitor Disperz while maintaining optimal therapeutic outcomes.

References

1. Everolimus. Drug Facts and Comparisons. eFacts [online]. 2021. Available from Wolters Kluwer Health, Inc.
2. Afinitor/Afinitor Disperz [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; February 2022.
3. NCCN Drugs & Biologics Compendium® Everolimus 2024. National Comprehensive Cancer Network, Inc. Accessed on January 24, 2024.
4. Royce M, Bachelot T, Villaneuva C, et al. Everolimus Plus Endocrine Therapy for Postmenopausal Women with Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-negative Advanced breast Cancer. JAMA Oncol. 2018;4(7): 977-984.

Policy History

Date	Action

October 2015	Addition to PA
December 2015	Annual review
March 2016	Addition of thymus neuroendocrine tumors that are metastatic or unresectable progressive disease; gastrointestinal (GI) neuroendocrine tumors that are metastatic or unresectable progressive disease; osteosarcoma that patient has previously been treated with an first-line therapy agent and used in combination with sorafenib; thymomas / thymic carcinomas that patient has previously been treated with an first-line therapy agent Removal of patient has had disease progression after treatment with sunitinib or sorafenib Policy number changed from 5.04.62 to 5.21.62
June 2016	Annual review
June 2017	Annual editorial review and reference update Addition of age limits to renewal criteria
February 2018	Addition of the following indications: Thyroid carcinoma that expresses one of the following histologies: Papillary, Hürthle cell, Follicular thyroid carcinoma; Gastrointestinal Stromal Tumors (GIST) with following requirements: Used in combination with either imatinib, sunitinib, or regorafenib, and disease progression after single-agent therapy with imatinib, sunitinib, and regorafenib; Endometrial carcinoma used in combination with letrozole Addition of the following requirement to Renal Cell Carcinoma with one of the following: Disease is of non-clear cell histology, or Disease is of predominantly clear cell histology and has progressed on prior antiangiogenic therapy Addition of quantity limits Removal of the Renal Cell Carcinoma requirement of has had disease progression after treatment with sunitinib or sorafenib
March 2018	Annual review
May 2018	Addition of the diagnosis TSC associated partial seizures for patients 2 years of age and older for Afinitor Disperz.
June 2018	Annual review
June 2019	Annual review and reference update
December 2019	Annual review
March 2020	Annual review and reference update
June 2020	Annual review and reference update
September 2020	Annual review
December 2020	Annual review. Added requirement that brand Afinitor 2.5mg, 5mg, 7.5mg has to t/f the preferred product everolimus
March 2021	Annual editorial review and reference update
June 2021	Annual editorial review and reference update

October 2021	Revised Afinitor requirement Advanced HR-positive, HER2 negative breast cancer from “Used in combination with exemestane” to “Used in combination with endocrine agent (e.g., exemestane, fulvestrant, or tamoxifen)” per reconsideration review
December 2021	Annual review and reference update. Added requirement that brand Afinitor 10mg and Afinitor Disperz all strengths must t/f the preferred product everolimus
March 2022	Annual review and reference update. Revised Afinitor quantity limits to account for new package sizes
December 2022	Annual review and reference update. Changed policy number to 5.21.062
March 2023	Annual review and reference update
March 2024	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 8, 2024 and is effective on April 1, 2024.