

Reference number
2021-A

SPECIALTY GUIDELINE MANAGEMENT

AFINITOR (everolimus) AFINITOR DISPERZ (everolimus) everolimus (generic)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications

1. Hormone Receptor-Positive, HER2-Negative Breast Cancer
Afinitor is indicated for the treatment of postmenopausal women with advanced hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole.
2. Neuroendocrine Tumors (NET)
 - a. Afinitor is indicated for the treatment of adult patients with progressive neuroendocrine tumors of pancreatic origin (PNET) with unresectable, locally advanced or metastatic disease.
 - b. Afinitor is indicated for the treatment of adult patients with progressive, well-differentiated, non-functional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin with unresectable, locally advanced or metastatic disease.
3. Renal Cell Carcinoma (RCC)
Afinitor is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib.
4. Tuberous Sclerosis Complex (TSC)-Associated Renal Angiomyolipoma
Afinitor is indicated for the treatment of adult patients with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery.
5. Tuberous Sclerosis Complex (TSC)-Associated Subependymal Giant Cell Astrocytoma (SEGA)
Afinitor and Afinitor Disperz are indicated in adult and pediatric patients aged 1 year and older with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.
6. Tuberous Sclerosis Complex (TSC)-Associated Partial-Onset Seizures
Afinitor Disperz is indicated for the adjunctive treatment of adult and pediatric patients aged 2 years and older with TSC-associated partial-onset seizures.

B. Compendial Uses

1. Relapsed or stage IV renal cell carcinoma:
 - a. Single agent or in combination with lenvatinib as subsequent therapy for clear cell histology
 - b. Single-agent systemic therapy for non-clear histology
 - c. In combination with lenvatinib as systemic therapy for non-clear cell histology
 - d. In combination with bevacizumab as systemic therapy for non-clear cell histology
2. Soft tissue sarcoma subtypes:
 - a. Perivascular epithelioid cell tumors (PEComa), single-agent therapy
 - b. Recurrent angiomyolipoma, single-agent therapy
 - c. Lymphangioliomyomatosis, single-agent therapy

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3. Gastrointestinal stromal tumors (GIST), therapy for unresectable, recurrent, or metastatic disease in combination with either imatinib, sunitinib, or regorafenib after failure on approved therapies
4. Neuroendocrine tumors:
 - a. Neuroendocrine tumors of the gastrointestinal tract, lung and thymus (carcinoid tumors)
 - b. Neuroendocrine tumors of the pancreas
 - c. Well differentiated Grade 3 neuroendocrine tumors
5. Thymomas and thymic carcinomas, as a single agent
6. Classic Hodgkin lymphoma, third-line or subsequent systemic therapy as a single agent for relapsed or refractory disease
7. Central nervous system cancers:
 - a. Meningiomas
 - b. Glioma
 - c. Subependymal giant cell astrocytoma (SEGA); adjuvant treatment as a single agent
8. Thyroid carcinoma (papillary carcinoma, Hürthle cell carcinoma, and follicular carcinoma), if clinical trials or other systemic therapies are not available or appropriate for treatment of progressive and/or symptomatic disease, not amenable to radioactive iodine (RAI) therapy
9. Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma, single-agent therapy for previously treated disease
10. Endometrial carcinoma, in combination with letrozole
11. Invasive breast cancer, as second-line therapy and beyond for recurrent or stage IV (M1) hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer in combination with exemestane, fulvestrant, or tamoxifen.
12. Tuberous sclerosis complex
13. Histiocytic Neoplasms:
 - a. Erdheim-Chester Disease (ECD)
 - b. Langerhans Cell Histiocytosis (LCH)
 - c. Rosai-Dorfman Disease

All other indications are considered experimental/investigational and not medically necessary.

II. DOCUMENTATION

Submission of the following information is necessary to initiate the prior authorization review: Documentation of the presence of phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutation (where applicable).

III. CRITERIA FOR INITIAL APPROVAL

A. Breast Cancer

Authorization of 12 months may be granted for subsequent treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative recurrent or metastatic breast cancer when prescribed in combination with exemestane, fulvestrant, or tamoxifen.

B. Renal Cell Carcinoma

Authorization of 12 months may be granted for treatment of relapsed, advanced, or stage IV renal cell carcinoma when any of the following criteria are met:

1. The requested medication is given as a single agent or in combination with lenvatinib as subsequent therapy for clear cell histology; OR

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2. The requested medication is given as single-agent or in combination with lenvatinib or bevacizumab for non-clear cell histology.

C. Neuroendocrine Tumors

Authorization of 12 months may be granted for the treatment of the following neuroendocrine tumors:

1. Neuroendocrine tumors of the gastrointestinal tract, lung, and thymus (carcinoid tumors)
2. Neuroendocrine tumors of the pancreas
3. Well differentiated Grade 3 neuroendocrine tumors

D. Tuberous Sclerosis Complex (TSC)

Authorization of 12 months may be granted for treatment of TSC.

E. Soft Tissue Sarcoma

Authorization of 12 months may be granted for treatment of any of the following subtypes of soft tissue sarcoma as single agent therapy: perivascular epithelioid cell (PEComa), recurrent angiomyolipoma, or lymphangiomyomatosis.

F. Gastrointestinal Stromal Tumor (GIST)

Authorization of 12 months may be granted for treatment of unresectable, recurrent, or metastatic GIST in combination with either imatinib, sunitinib, or regorafenib for members who have failed at least four FDA-approved therapies (e.g., imatinib, sunitinib, regorafenib, ripretinib)

G. Thymoma and Thymic Carcinoma

Authorization of 12 months may be granted for treatment of thymoma or thymic carcinoma as a single agent.

H. Classic Hodgkin Lymphoma

Authorization of 12 months may be granted for treatment of relapsed or refractory classic Hodgkin lymphoma for third-line or subsequent systemic therapy as a single agent.

I. Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma

Authorization of 12 months may be granted for treatment of Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma as a single-agent therapy for previously treated disease.

J. Papillary, Hürthle cell, or Follicular Thyroid Carcinoma

Authorization of 12 months may be granted for treatment of progressive and/or symptomatic papillary, Hürthle cell, or follicular thyroid carcinoma not amenable to radioactive iodine (RAI) therapy.

K. Endometrial Carcinoma

Authorization of 12 months may be granted for treatment of endometrial carcinoma in combination with letrozole.

L. Central Nervous System Cancers

Authorization of 12 months may be granted for treatment of the following central nervous system cancers:

1. Glioma (including glioblastoma) or meningioma
2. Adjuvant treatment of subependymal giant cell astrocytoma (SEGA) as a single agent

M. Histiocytic Neoplasms

Authorization of 12 months may be granted for the treatment of any of the following histiocytic neoplasm subtypes as a single agent in members with a phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutation:

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1. Symptomatic or relapsed/refractory Erdheim-Chester Disease (ECD)
2. Symptomatic or relapsed/refractory Rosai-Dorfman Disease
3. Langerhans Cell Histiocytosis (LCH)

IV. CONTINUATION OF THERAPY

Authorization of 12 months may be granted for continued treatment in members requesting reauthorization for an indication in Section III when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

V. REFERENCES

1. Afinitor and Afinitor Disperz [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2021.
2. Everolimus [package insert]. Chestnut Ridge, NY: Par Pharmaceutical; May 2020.
3. The NCCN Drugs & Biologics Compendium 2021 National Comprehensive Cancer Network, Inc. <https://www.nccn.org>. Accessed May 6, 2021.
4. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor–positive advanced breast cancer. *N Engl J Med*. 2012;366(6):520-529.
5. Yardley DA, Noguchi S, Pritchard KI, et al. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. *Adv Ther* 2013;30:870-884.
6. Sampson JR. Therapeutic targeting of mTOR in tuberous sclerosis. *Biochem Soc Trans*. 2009;37:259-264.
7. Johnston PB, Inwards DJ, Colgan JP, et al. A Phase II trial of the oral mTOR inhibitor everolimus in relapsed Hodgkin lymphoma. *Am J Hematol* 2010;85:320-324.
8. Darcy A. Krueger, Hope Northrup, et al. Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatric Neurology*. 2013. 49: 255-265.
9. Wahl Michael, Chang, Susan, et al. Probing the PI3K/mTOR Pathway in Gliomas: A Phase II Study of Everolimus for Recurrent Adult Low Grade Gliomas. *Cancer*. 2017; 123 (23): 4631-4639.
10. Shih KC, Chowdhary S, et al. A Phase II trial of bevacizumab and everolimus as treatment for patients with refractory, progressive, intracranial meningioma. *Journal of Neuro-Oncology*. 2016. 129 (2): 281-8.
11. Hainsworth, John D, et al. Phase II Study of concurrent radiation therapy, temozolomide, and bevacizumab followed by bevacizumab/everolimus as first-line treatment of patients with glioblastoma. *Clin adv Hematol. Oncol*. 2012. 10 (4): 240-6.