Drug Coverage Policy

Effective Date.....6/15/2025
Coverage Policy Number.....IP0408
Policy Title....Everolimus Products

Oncology - Everolimus Products

- **Afinitor® (everolimus tablets – Novartis, generic)**
- **Afinitor Disperz® (everolimus tablets for oral suspension – Novartis)**
- **Torpenz™ (everolimus tablets – Upsher-Smith)**

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

OVERVIEW

Afinitor, a kinase inhibitor, is indicated for the following uses:[1]

- **Breast cancer**, treatment of advanced hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative disease in combination with exemestane, after failure of treatment with letrozole or anastrozole in postmenopausal women.
- **Neuroendocrine tumors (NET)**, treatment of progressive disease of pancreatic origin and progressive, well-differentiated, non-functional NET of gastrointestinal or lung origin that are unresectable, locally advanced, or metastatic in adults. Limitation of Use: Afinitor is not indicated for the treatment of patients with functional carcinoid tumors.
- **Renal cell carcinoma**, treatment of advanced disease after failure of treatment with sunitinib or sorafenib in adults.
- **Tuberous sclerosis complex (TSC)-associated renal angiomyolipoma,** treatment of adults not requiring immediate surgery.
- **TSC-associated subependymal giant cell astrocytoma (SEGA)**, treatment of patients ≥ 1 year of age who require therapeutic intervention but cannot be curatively resected.

Afinitor Disperz, a kinase inhibitor, is indicated for the following uses:[1]

- **TSC-associated SEGA**, treatment of patients ≥ 1 year of age who require therapeutic intervention but cannot be curatively resected.
- **TSC-associated partial-onset seizures**, adjunctive treatment of patients ≥ 2 years of age.

Torpenz, a kinase inhibitor, is indicated for the following uses:[2]

- **Breast cancer**, treatment of advanced HR+, HER2-negative disease in combination with exemestane, after failure of treatment with letrozole or anastrozole in postmenopausal women.
- **Renal angiomyolipoma and TSC,** treatment of adults not requiring immediate surgery.
- **TSC-associated SEGA**, treatment of patients ≥ 1 year of age who require therapeutic intervention but cannot be curatively resected.

Of note, Zortress® (everolimus tablets) is indicated in combination with other drugs for prophylaxis of organ rejection in adults undergoing kidney or liver transplant.[3] The tablet strengths and dosing are different for Zortress and Afinitor. Zortress is not targeted in this policy.

Guidelines

The National Comprehensive Cancer Network (NCCN) Compendium recommends use of everolimus for the indications listed in the FDA-Approved Indications and Other Uses with Supportive Evidence sections.[4]

Coverage Policy

POLICY STATEMENT

Prior Authorization is required for prescription benefit coverage of everolimus products. All approvals are provided for the duration noted below. In the clinical criteria, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: a woman is defined as an individual with the biological traits of a woman, regardless of the individual's gender identity or gender expression; men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

Everolimus products are considered medically necessary when ONE of the following are met:

FDA-Approved Indications

1. **Breast Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, F, G, and H):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has recurrent or metastatic, hormone receptor positive (HR+) [i.e., estrogen receptor-positive {ER+} and/or progesterone receptor-positive {PR+}] disease; AND
   - **C)** Patient has human epidermal growth factor receptor 2 (HER2)-negative breast cancer; AND
   - **D)** Patient has tried at least one prior endocrine therapy (e.g., anastrozole, letrozole, or tamoxifen); AND
   - **E)** Patient meets ONE of the following (i or ii):
     - **A)** Patient is a postmenopausal woman* or a man*; OR
     - **B)** Patient is a pre/perimenopausal woman* and meets ONE of the following (a or b):
       - **a)** Patient is receiving ovarian suppression/ablation with a gonadotropin-releasing hormone (GnRH) agonist; OR
         Note: Examples of a GnRH agonist include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant).
       - **b)** Patient has had surgical bilateral oophorectomy or ovarian irradiation; AND
   - **F)** Patient meets ONE of the following (i or ii):
     - **A)** The medication will be used in combination with exemestane and the patient meets ONE of the following (a or b):
       - **a)** Patient is a man* and the patient is receiving a gonadotropin-releasing hormone (GnRH) analog; OR
         Note: Examples of a GnRH analog include leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous implant), Firmagon (degarelix acetate subcutaneous injection), and Orgovyx (relugolix tablet).
       - **b)** Patient is a woman*; OR
     - **B)** The medication will be used in combination with fulvestrant or tamoxifen; AND
   - **G)** Patient has not had disease progression while on everolimus.
   - **H)** Preferred product criteria is met for the product(s) as listed in the below table(s)

   *Refer to the Policy Statement.

2. **Neuroendocrine Tumors of the Pancreas, Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors).** Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** Patient is ≥ 18 years of age.
   - **B)** Preferred product criteria is met for the product(s) as listed in the below table(s)

3. **Renal Cell Carcinoma.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has relapsed or Stage IV disease; AND
   - **C)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has non-clear cell disease; OR
     - **ii.** Patient meets BOTH of the following (a and b):
       - **a)** Patient has clear cell disease; AND
       - **b)** Patient has tried at least one prior systemic therapy.
         Note: Examples of prior systemic therapy include the following products: Inlyta (axitinib tablets), Lenvima (lenvatinib capsules), Cabometyx (cabozantinib tablets), Keytruda (pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), pazopanib, sunitinib.

D) Preferred product criteria are met for the product(s) as listed in the below table(s).

4. **Tuberous Sclerosis Complex-Associated Renal Angiomyolipoma.** Approve for 1 year if the patient meets the following (A):

A.) Preferred product criteria are met for the product(s) as listed in the below table(s).

5. **Tuberous Sclerosis Complex-Associated Subependymal Giant Cell Astrocytoma (SEGA).** Approve for 1 year if the patient meets BOTH of the following (A and B)
   - **A.** Therapeutic intervention is required but SEGA cannot be curatively resected
   - **B.** Preferred product criteria are met for the product(s) as listed in the below table(s).

6. **Tuberous Sclerosis Complex-Associated Partial Onset Seizures.** Approve for 1 year if the patient meets the following (A):

A.) Preferred product criteria are met for the product(s) as listed in the below table(s).

Other Uses with Supportive Evidence

1. **Endometrial Carcinoma.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** The medication will be used in combination with letrozole.
   - **C)** Preferred product criteria are met for the product(s) as listed in the below table(s).

2. **Gastrointestinal Stromal Tumors.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has tried each of the following (i, ii, iii, and iv):
     - **i.** One of imatinib or Ayvakit (avapritinib tablets); AND
     - **ii.** One of sunitinib or Sprycel (dasatinib tablets); AND
     - **iii.** Stivarga (regorafenib tablets); AND
     - **iv.** Qinlock (ripretinib tablets); AND
   - **C)** The medication will be used in combination with imatinib, sunitinib, or Stivarga (regorafenib tablets).
   - **D)** Preferred product criteria are met for the product(s) as listed in the below table(s).

3. **Histiocytic Neoplasm.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets ONE of the following (i, ii, or iii):
     - **i.** Patient has Langerhans cell histiocytosis; OR
     - **ii.** Patient has Erdheim-Chester disease; OR
     - **iii.** Patient has Rosai-Dorfman disease; AND
   - **C)** Patient has a *PIK3CA* mutation.
   - **D)** Preferred product criteria are met for the product(s) as listed in the below table(s).

4. **Classic Hodgkin Lymphoma.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has relapsed or refractory disease; AND
   - **C)** Patient is not a candidate for high-dose therapy and autologous stem cell rescue.

D) Preferred product criteria are met for the product(s) as listed in the below table(s).

5. **Meningioma.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has recurrent or progressive disease; AND
   C) Patient meets BOTH of the following: (i and ii):
      i. Patient has surgically inaccessible disease; AND
      ii. Radiation therapy is not possible.
   D) Patient meets ONE of the following (i or ii):
      i. The medication will be used in combination with a somatostatin analogue; OR
      Note: Example of somatostatin analogue includes octreotide.
      ii. The medication will be used in combination with bevacizumab.
   E) Preferred product criteria are met for the product(s) as listed in the below table(s).

6. **Soft Tissue Sarcoma.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has ONE of the following (i or ii):
      i. Perivascular epithelioid cell tumor (PEComa); OR
      ii. Recurrent angiomyolipoma/lymphangioleiomyomatosis.
   C) Preferred product criteria are met for the product(s) as listed in the below table(s).

7. **Thymomas and Thymic Carcinomas.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets ONE of the following (i or ii):
      i. Patient has tried at least one chemotherapy regimen; OR
      Note: Examples of a chemotherapy regimen include cisplatin, doxorubicin, and cyclophosphamide; cisplatin plus etoposide; carboplatin plus paclitaxel; carboplatin, paclitaxel, and Cyramza (ramucirumab intravenous infusion).
      ii. Patient cannot tolerate chemotherapy.
   C) Preferred product criteria are met for the product(s) as listed in the below table(s).

8. **Thyroid Carcinoma, Differentiated.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has differentiated thyroid carcinoma; AND
   Note: Examples of differentiated thyroid carcinoma include papillary, follicular, and oncocytic thyroid carcinoma.
   C) The disease is refractory to radioactive iodine therapy.
   D) Preferred product criteria are met for the product(s) as listed in the below table(s).

9. **Uterine Sarcoma**. Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has advanced, recurrent, metastatic, or inoperable disease; AND
   C) Patient has a perivascular epithelioid cell tumor (PEComa); AND
   D) Patient has tried at least one systemic regimen.

Note: Examples of systemic regimen include doxorubicin, docetaxel, gemcitabine, ifosfamide, dacarbazine.

E) Preferred product criteria are met for the product(s) as listed in the below table(s).

10. Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):

A) Patient is ≥ 18 years of age; AND

B) Patient has tried at least one systemic regimen.
Note: Examples of a systemic regimen include one or more of the following agents: bortezomib, bendamustine, rituximab, cyclophosphamide, Imbruvica (ibrutinib capsules, tablets, and oral solution), Brukinsa (zanubrutinib capsules), Kyprolis (carfilzomib intravenous infusion), or Ninlaro (ixazomib capsules).

C) Preferred product criteria are met for the product(s) as listed in the below table(s).

Employer Plans:

Product	Criteria
Afinitor tablets (everolimus)	The following: 1. Trial of **everolimus tablets** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction
Afinitor Disperz (everolimus tablets for oral suspension)	The following: 1. Trial of **everolimus tablets for oral suspension** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction

Individual and Family Plans:

Product	Criteria
Afinitor tablets (everolimus)	The following: 1. Trial of **everolimus tablets** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction
Afinitor Disperz (everolimus tablets for oral suspension)	The following: 1. Trial of **everolimus tablets for oral suspension** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based

literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Everolimus products for any other use is considered not medically necessary. Criteria will be updated as new published data are available.

References

1. Afinitor® tablets, Afinitor Disperz® tablets for oral suspension [prescribing information]. East Hanover, NJ: Novartis; January 2025.
2. Torpenz™ tablets [prescribing information]. Maple Grove, MN: Upsher-Smith; March 2024.
3. Zortress® tablets [prescribing information]. East Hanover, NJ: Novartis; February 2024.
4. The NCCN Drugs & Biologics Compendium. © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 13, 2025. Search term: everolimus.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Updated** coverage policy title. **Tuberous Sclerosis Complex-Associated Renal Angiomyolipoma.** • **Removed** criterion screening for age. • **Removed** criterion requiring confirmation of angiomyolipoma greater than or equal to 3 cm diagnosed on radiographic imaging. **Tuberous Sclerosis Complex-Associated Partial Onset Seizures.** • **Removed** criterion screening for age. • **Removed** criteria requiring failure, contraindication, or intolerance to two antiepileptic drugs. • **Removed** criterion requiring use as adjunctive therapy to other antiepileptic drugs. • **Removed** criterion requiring consultation with specialist.	6/15/2024
Annual Revision	**Updated title from** "Everolimus Products for Non-Oncology Uses" **to** "Oncology – Everolimus Products" **Added** Torpenz™ (everolimus tablets – Upsher-Smith) **FDA-Approved Indications.**	6/15/2025

	Added the following: Breast Cancer, Neuroendocrine Tumors of the Pancreas, Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors), Renal Cell Carcinoma, Tuberous Sclerosis Complex-Associated Subependymal Giant Cell Astrocytoma (SEGA). **Other Uses with Supportive Evidence.** **Added the following**: Endometrial Carcinoma, Gastrointestinal Stromal Tumors, Histiocytic Neoplasm, Classic Hodgkin Lymphoma, Meningioma, Soft Tissue Sarcoma, Thymomas and Thymic Carcinomas, Thyroid Carcinoma, Differentiated, Uterine Sarcoma, Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma.	

The policy effective date is in force until updated or retired.