

Clinical Policy: Everolimus (Afinitor, Afinitor Disperz, Zortress)

Reference Number: PA.CP.PHAR.63

Effective Date: 01/18

Last Review Date: 01/19

[Coding Implications](#)

[Revision Log](#)

Description

Everolimus (Afinitor[®], Afinitor Disperz[®], Zortress[®]) is an mTOR kinase inhibitor.

FDA Approved Indication(s)

| Indication | Afinitor | Afinitor Disperz | Zortress |
|---|----------------------|-----------------------|------------|
| <i>Labeled uses (and recommended NCCN uses by product as indicated)</i> | | | |
| Breast cancer | X - adults | X - adults per NCCN | --- |
| PNET (pancreas) | X - adults | X - adults per NCCN | --- |
| NET (GI, lung, thymic-off-label) | X - adults | X - adults per NCCN | --- |
| RCC | X - adults | X - adults per NCCN | --- |
| TSC-AML (renal) | X - adults | X - adults per NCCN | --- |
| TSC-SEGA | X - 1 year and older | X - 1 year and older | --- |
| TSC-seizures | --- | X - 2 years and older | --- |
| Prophylaxis of organ rejection | --- | --- | X - adults |
| <i>Recommended NCCN uses (adults)</i> | | | |
| Meningioma | X | X | --- |
| HL | X | X | --- |
| STS-GIST | X | X | --- |
| STS-PEComa, angiomyolipoma, lymphangioleiomyomatosis | X | X | --- |
| Thymoma/thymic carcinoma | X | X | --- |
| DTC | X | X | --- |
| WM/LPL | X | X | --- |
| Endometrial carcinoma | X | X | --- |

Abbreviations: DTC (differentiated thyroid carcinoma), GI (gastrointestinal), HL (Hodgkin lymphoma), PNET (pancreatic neuroendocrine tumor), NET (neuroendocrine tumors), RCC (renal cell carcinoma), STS-GIST (soft tissue sarcoma-gastrointestinal stromal tumor), STS-PEComa (soft tissue sarcoma-perivascular epithelioid cell tumor), TSC-AML (tuberous sclerosis complex- angiomyolipoma), TSC-SEGA (tuberous sclerosis complex-subependymal giant cell astrocytoma), TSC-seizures (tuberous sclerosis complex-seizures). WM/LPL (Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma)

Afinitor is indicated for the treatment of:

- Adult patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib.
- Adult patients 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.

Limitation(s) of use: Afinitor is not indicated for the treatment of patients with functional carcinoid tumors.

- Adult patients with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery.

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

Afinitor and Afinitor Disperz are indicated for the treatment of 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.

Afinitor Disperz is indicated for the adjunctive treatment of adult and pediatric patients aged 2 years and older with TSC-associated partial-onset seizures.

Zortress is indicated for the prophylaxis of organ rejection in adult patients:

- Kidney transplant: at low-moderate immunologic risk. Use in combination with basiliximab, cyclosporine (reduced doses) and corticosteroids.
- Liver transplant: administer no earlier than 30 days post-transplant. Use in combination with tacrolimus (reduced doses) and corticosteroids.

Limitation(s) of use: Safety and efficacy of Zortress have not been established in the following:

- Kidney transplant patients at high immunologic risk
- Recipients of transplanted organs other than kidney or liver
- Pediatric patients (less than 18 years)

Policy/Criteria

It is the policy of health plans affiliated with Pennsylvania Health and Wellness® that everolimus is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Breast Cancer (must meet all):

1. Diagnosis of recurrent or metastatic breast cancer;
2. Prescribed by or in consultation with an oncologist;
3. Disease is hormone-receptor positive and Human epidermal growth factor receptor 2 (HER2)-negative;
4. Prior history of endocrine therapy (Appendix B) unless contraindicated or clinically significant adverse effects are experienced;
5. Prescribed in combination with exemestane (Aromasin), fulvestrant or tamoxifen;
6. Request is for Afinitor or Afinitor Disperz;
7. Request meets one of the following (a or b):
 - a. Dose does not exceed 10 mg per day (1 tablet per day);
 - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

B. Neuroendocrine Tumor (must meet all):

1. Diagnosis of NET of one of the following origins:

- a. Pancreatic;
 - b. GI tract;
 - c. Lung;
 - d. Thymus (off-label)
2. Prescribed by or in consultation with an oncologist;
3. Disease is unresectable, locally advanced or metastatic;
4. Request is for Afinitor or Afinitor Disperz;
5. Request meets one of the following (a or b):
 - c. Dose does not exceed 10 mg per day (1 tablet per day);
 - d. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

C. Renal Cell Carcinoma (must meet all):

1. Diagnosis of relapsed stage IV (unresectable or metastatic) RCC;
2. Prescribed by or in consultation with an oncologist;
3. If clear cell histology, failure of a prior therapy (Appendix B) unless contraindicated or clinically significant adverse effects are experienced;
**Prior authorization may be required.*
4. Request is for Afinitor or Afinitor Disperz;
5. Request meets one of the following (a or b):
 - a. Dose does not exceed 10 mg per day (1 tablet per day);
 - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

D. Renal Angiomyolipoma and Other PEComas (must meet all):

1. Diagnosis of renal angiomyolipoma associated with TSC, not requiring immediate surgery;
2. Prescribed by or in consultation with an oncologist;
3. Request is for Afinitor or Afinitor Disperz;
4. Request meets one of the following (a or b):
 - a. Dose does not exceed 10 mg per day (1 tablet per day);
 - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

E. Tuberous Sclerosis Complex with Subependymal Giant Cell Astrocytoma (must meet all):

1. Diagnosis of subependymal giant cell astrocytoma (SEGA) associated with TSC;
2. Prescribed by or in consultation with an oncologist;
3. Member is not a candidate for curative surgical resection;
4. Request is for Afinitor or Afinitor Disperz;
5. Request meets one of the following (a or b):

- a. Initial dosing does not exceed 5 mg/m² per day;
- b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

F. Tuberous Sclerosis Complex-Associated Partial-Onset Seizures (must meet all):

1. Diagnosis of partial-onset seizures associated with TSC;
2. Prescribed by or in consultation with an oncologist;
3. Request is for Afinitor Disperz.

Approval duration: 6 months

G. Prophylaxis of Organ Rejection (must meet all):

1. Member has received or is scheduled for a kidney or liver transplant;
2. Prescribed by or in consultation with a nephrologist, hepatologist, or transplant specialist;
3. For kidney transplant (must meet a or b):
 - a. Failure of tacrolimus unless contraindicated or clinically significant adverse effects are experienced; or
 - b. Currently taking and stabilized on everolimus;
4. Request is for Zortress;
5. Prescribed in combination with one of the following (a or b):
 - a. For kidney transplant: Simulect®, cyclosporine, and corticosteroids;
 - b. For liver transplant: tacrolimus and corticosteroids.

Approval duration: 6 months

H. NCCN Compendium Indications (off-label) (must meet all):

1. Diagnosis of one of the following (a, b, c, d, or e):
 - a. Meningioma, HL, WM/LPL, thymoma, or thymic carcinoma (refractory, recurrent or progressive disease);
 - b. PEComa, angiomyolipoma (recurrent), or lymphangioleiomyomatosis;
 - c. Endometrial carcinoma (in combination with letrozole);
 - d. Gastrointestinal stromal tumors (GIST) (in combination with imatinib, Sutent®, or Stivarga® for disease progression after single agent therapy with imatinib, Sutent, and Stivarga®)*;

**Prior authorization may be required.*

 - e. DTC (i.e., follicular, Hurthle cell or papillary carcinoma; failure of Lenvima® or Nexavar® unless contraindicated or clinically significant adverse effects are experienced);

**Prior authorization may be required.*
2. Prescribed by or in consultation with an oncologist;
3. Request is for Afinitor or Afinitor Disperz;
4. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

I. Other diagnoses/indications:

1. Refer to PA.CP.PMN.53

II. Continued Approval

A. All Indications Specifically Addressed in Section I (Initial Approval Criteria) (must meet all):

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy (e.g., no disease progression or unacceptable toxicity);
3. If request is for a dose increase, request meets one of the following (a or b):
 - a. New dose does not exceed 10 mg/day;
 - b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

B. Other diagnoses/indications (1 or 2):

1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies.

Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to PA.CP.PMN.53

Background

Description/Mechanism of Action:

Everolimus is an inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers. Inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in *in vitro* or *in vivo* studies.

Formulations:

Afinitor - oral tablets

2.5, 5, 7.5 and 10 mg tablets

Afinitor Disperz - tablets for oral suspension

2, 3, 5 mg tablets

Appendices

Appendix A: Abbreviation/Acronym Key

AML: angiomyolipoma

ER: estrogen receptor

DTC: differentiated thyroid cancer

FDA: Food and Drug Administration

GI: gastrointestinal
GIST: gastrointestinal stromal tumor
HER-2: human epidermal growth factor receptor-2
HL: Hodgkin lymphoma
HR: hormone receptor
NET: neuroendocrine tumor
PEComa: perivascular epithelioid cell tumor
PNET: pancreatic neuroendocrine tumor

RCC: renal cell carcinoma
SEGA: subependymal giant cell astrocytoma
TSC: tuberous sclerosis complex
WM/LPL: Waldenström macroglobulinemia/lymphoplasmacytic lymphoma

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|----------------|-----------------------------|
| <i>Breast Cancer: Examples of endocrine therapies per NCCN</i> | | |
| <ul style="list-style-type: none"> Nonsteroidal aromatase inhibitors (anastrozole and letrozole); Steroidal aromatase inhibitors (exemestane) Serum estrogen receptor (ER) modulators (tamoxifen, toremifene) ER down-regulators (fulvestrant) Progestin (megestrol acetate) Androgens (fluoymesterone) High-dose estrogen (ethinyl estradiol) | Varies | Varies |
| <i>RCC: Examples of first and second-line therapies for relapsed or stage IV disease per NCCN</i> | | |
| <ul style="list-style-type: none"> Votrient® (pazopanib) Sutent® (sunitinib) Opdivo® (nivolumab) ± Yervoy® (ipilimumab) Avastin® (bevacizumab) ± (Intron A (interferon alfa-2b), Tarceva (erlotinib) or Afinitor/Afinitor Disperz (everolimus)) Proleukin® (aldesleukin) Cabometyx® (cabozantinib) Torisel® (temsirolimus) Inlyta® (axitinib) Afinitor/Afinitor Disperz (everolimus) ± Lenvima (lenvatinib) Nexavar (sorafenib) Tarceva® (erlotinib) | Varies | Varies |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|------------------------|---------------------|-----------------------------|
| GIST | | |
| imatinib (Gleevec®) | 400 mg PO QD or BID | 800 mg/day |
| Sutent (sunitinib) | 50 mg PO QD | 50 mg/day |
| Stivarga (regorafenib) | 160 mg PO QD | 160 mg/day |
| DTC | | |
| Lenvima (lenvatinib) | 24 mg PO QD | 24 mg/day |
| Nexavar (sorafenib) | 400 mg PO QD | 400 mg/day |

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Afinitor and Afinitor Disperz are contraindicated in patients with clinically significant hypersensitivity to everolimus or to other rapamycin derivatives.
- Zortress is contraindicated in patients with known hypersensitivity to everolimus, sirolimus, or to components of the drug product.
- Boxed warning(s) for Zortress: malignancies and serious infections, kidney graft thrombosis, nephrotoxicity and mortality in heart transplantation.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

| HCPCS Codes | Description |
|-------------|--------------------------|
| J7527 | Everolimus, oral, 0.25mg |

| Reviews, Revisions, and Approvals | Date | Approval Date |
|---|-------|---------------|
| Removed dose form requirement by indication, no clinical difference expected (dosing is equivalent for SEGA indication). For RCC, included list of first line therapies per NCCN guidelines. For breast cancer, removed compendium supported use after tamoxifen as this was removed from the 1.2017 NCCN guideline update. Added the following off-label NCCN compendium supported uses: GIST, lymphoplasmacytic lymphoma, osteosarcoma, endometrial carcinoma. References reviewed and updated. | 02/18 | |
| 1Q 2019 annual review; age added for oncology indications; breast cancer - prior therapy changed from aromatase inhibitor to endocrine therapy and combination therapy expanded to include fulvestrant or tamoxifen per NCCN; RCC prior therapy broadened to encompass NCCN listed therapies; TSC-seizures limited to Afinitor Disperz per label; section G off-label uses - | 01/19 | |

| Reviews, Revisions, and Approvals | Date | Approval Date |
|--|------|---------------|
| meningioma added, osteosarcoma removed, prior therapy added for DTC per NCCN; references reviewed and updated. | | |
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References

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