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

Reference Number: ERX.SPA.57
Effective Date: 10.01.16
Last Review Date: 02.21
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

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

FDA Approved Indication(s)

Indication	Afinitor	Afinitor Disperz	Zortress
Labeled uses (and recommended NCCN uses by product as indicated)			
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
Recommended NCCN uses (adults)			
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-subepndymal giant cell astrocytoma), TSC-seizures (tuberous sclerosis complex-seizures). WM/LPL (Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma)

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 (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole.
- 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 advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib.
- Adult patients with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery.

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
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Afinitor, Afinitor Disperz, and Zortress are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Breast Cancer (must meet all)**:**
1. Request is for Afinitor or Afinitor Disperz;
2. Diagnosis of recurrent or metastatic breast cancer;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. For Afinitor or Afinitor Disperz request, medical justification supports inability to use everolimus, if available (e.g., contraindications to excipients);
6. Disease is HR-positive and HER2-negative;
7. History of endocrine therapy (see *Appendix B*) unless contraindicated or clinically significant adverse effects are experienced;
8. Prescribed in combination with exemestane, fulvestrant, or tamoxifen;
9. Request meets one of the following (a or b):*
   a. Dose does not exceed 20 mg (2 tablets Afinitor or 4 tablets Afinitor Disperz) per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:
Commercial – Length of Benefit
Medicaid – 6 months

B. Neuroendocrine Tumor (must meet all)**:**
1. Request is for Afinitor or Afinitor Disperz;
2. Diagnosis of NET of one of the following origins (a – e):
   a. Pancreatic;
   b. GI tract;
   c. Lung;
   d. Thymus (off-label);
   e. Bronchopulmonary (off-label);

3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. For Afinitor or Afinitor Disperz request, medical justification supports inability to use everolimus, if available (e.g., contraindications to excipients);
6. Disease is unresectable, locally advanced, or metastatic;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 20 mg (2 tablets Afinitor or 4 tablets Afinitor Disperz) per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:
Commercial – Length of Benefit
Medicaid – 6 months

C. Renal Cell Carcinoma (must meet all)**:**
1. Request is for Afinitor or Afinitor Disperz;
2. Diagnosis of relapsed or stage IV (unresectable or metastatic disease) RCC;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. For Afinitor or Afinitor Disperz request, medical justification supports inability to use everolimus, if available (e.g., contraindications to excipients);
6. If clear cell histology, failure of a prior therapy (see *Appendix B*) unless contraindicated or clinically significant adverse effects are experienced;

   **Prior authorization may be required for prior therapies*
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 20 mg (2 tablets Afinitor or 4 tablets Afinitor Disperz) per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:
Commercial – Length of Benefit
Medicaid – 6 months

D. Renal Angiomyolipoma with Tuberous Sclerosis Complex (must meet all)**:**
1. Request is for Afinitor or Afinitor Disperz;
2. Diagnosis of renal angiomyolipoma associated with TSC, not requiring immediate surgery;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. For Afinitor or Afinitor Disperz request, medical justification supports inability to use everolimus, if available (e.g., contraindications to excipients);
6. Request meets one of the following (a or b)*:
   a. Dose does not exceed 20 mg (2 tablets Afinitor or 4 tablets Afinitor Disperz) per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:
Commercial – Length of Benefit
Medicaid – 6 months

E. Tuberous Sclerosis Complex with Subependymal Giant Cell Astrocytoma (must meet all)**:**
1. Request is for Afinitor or Afinitor Disperz;
2. Diagnosis of SEGA associated with TSC;
3. Prescribed by or in consultation with an oncologist;
4. For Afinitor or Afinitor Disperz request, medical justification supports inability to use everolimus, if available (e.g., contraindications to excipients);
5. Member is not a candidate for curative surgical resection.

Approval duration:
Commercial – Length of Benefit
Medicaid – 6 months

F. Tuberous Sclerosis Complex-Associated Partial-Onset Seizures (must meet all)**:**
1. Request is for Afinitor Disperz;
2. Diagnosis of partial-onset seizures associated with TSC;
3. For Afinitor Disperz request, medical justification supports inability to use everolimus, if available (e.g., contraindications to excipients);
4. Prescribed by or in consultation with an oncologist or neurologist.

Approval duration:
Commercial – Length of Benefit
Medicaid – 6 months

G. Prophylaxis of Organ Rejection (must meet all)**:**
1. Request is for Zortress;
2. Member has received or is scheduled for a kidney or liver transplant;
3. Prescribed by or in consultation with a nephrologist, hepatologist, or transplant specialist;
4. Age ≥ 18 years;
5. For Zortress request, medical justification supports inability to use everolimus, if available (e.g., contraindications to excipients);
6. For kidney transplant, failure of tacrolimus unless contraindicated or clinically significant adverse effects are experienced;
7. 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:
Commercial – Length of Benefit
Medicaid – 6 months

H. NCCN Compendium Indications (off-label) (must meet all)**:**
1. Request is for Afinitor or Afinitor Disperz;
2. Diagnosis of one of the following (a, b, c, d, or e):
   a. HL, WM//LPL, thymoma, or thymic carcinoma (refractory, recurrent, progressive, unresectable, or metastatic disease, or disease not responding to previous therapy);
   b. PEComa, angiomyolipoma (recurrent), or lymphangioleiomyomatosis;
   c. Endometrial carcinoma (in combination with letrozole);
   d. GIST (in combination with imatinib, Sutent®, or Stivarga® for disease progression after therapy with imatinib, Sutent, and Stivarga);*
      **Prior authorization may be required for imatinib, Sutent, and Stivarga*
   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 for Lenvima and Nexavar*
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. For Afinitor or Afinitor Disperz request, medical justification supports inability to use everolimus, if available (e.g., contraindications to excipients);
6. 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*).*
   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:
Commercial – Length of Benefit
Medicaid – 6 months

I. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, or documentation supports that member is currently receiving Afinitor, Afinitor Disperz, or Zortress for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. For Afinitor, Afinitor Disperz, Zortress request, medical justification supports inability to use everolimus, if available (e.g., contraindications to excipients);
4. For all indications, except partial-onset seizures associated with TSC, SEGA associated with TSC, and organ rejection prophylaxis, if request is for a dose increase, request meets one of the following (a or b):*
   a. New dose does not exceed 20 mg (2 tablets Afinitor or 4 tablets Afinitor Disperz) per day;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:
Commercial – Length of Benefit
Medicaid – 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

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: subepndymal giant cell astrocytoma
TSC: tuberous sclerosis complex
WM/LPL: Waldenstrom 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
Breast cancer: Examples of endocrine therapies per NCCN		
• 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 (fluoxymesterone) • High-dose estrogen (ethinyl estradiol)	Varies	Varies
RCC: Examples of first and second-line therapies for relapsed or stage IV disease per NCCN		
• Votrient® (pazopanib) • Sutent® (sunitinib) • Opdivo® (nivolumab) ± Yervoy® (iplimumab) 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
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
- Contraindication(s):
  - Afinitor and Afinitor Disperz: clinically significant hypersensitivity to everolimus or to other rapamycin derivatives
  - Zortress: 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 when used in de novo patients within the first three months post-transplantation

Appendix D: General Information

- Heart transplant: Although the off-label use of Zortress in heart transplant is not supported by the Micromedex DrugDex compendium, it does have both literature and guideline support. Individual risk-benefit ratios must be considered prior to such use because of safety concerns (see Appendix C – boxed warnings). Examples of patient-specific scenarios where use may be appropriate include, but are not limited to: patient already established on therapy, refractory or recurrent rejection, renal insufficiency, cardiac allograft vasculopathy (CAV), history of malignancies, calcineurin inhibitor (CNI) toxicity.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Breast cancer, PNET (pancreas), NET (GI, lung), RCC, TSC-AML (renal)	Afinitor 10 mg PO QD	20 mg/day
TSA-SEGA	Afinitor/Afinitor Disperz 4.5 mg/m^2 PO QD; adjust dose to attain trough concentrations of 5-15 ng/mL	Based on trough concentrations
TSC-associated partial-onset seizures	Afinitor Disperz 5 mg/m^2 PO QD; adjust dose to attain trough concentrations of 5-15 ng/mL	Based on trough concentrations
Kidney transplant rejection prophylaxis	Zortress 0.75 mg PO BID; adjust dose to attain trough concentrations of 3 to 8 ng/mL	Based on trough concentrations
Liver transplant rejection prophylaxis	Zortress 1 mg PO BID; adjust dose to attain trough concentrations of 3 to 8 ng/mL	Based on trough concentrations

VI. Product Availability

Drug Name	Availability
Everolimus (Afinitor)	Tablets: 2.5 mg, 5 mg, 7.5 mg, 10 mg
Everolimus (Afinitor Disperz)	Tablets for oral suspension: 2 mg, 3 mg, 5 mg
Everolimus (Zortress)	Tablets: 0.25 mg, 0.5 mg, 0.75 mg, 1 mg

VII. References

1. Afinitor/Afinitor Disperz Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; March 2020. Available at: https://www.novartis.us/sites/www.novartis.us/files/afinitor.pdf. Accessed October 13, 2020.
2. Zortress Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; August 2018. Available at: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/zortress.pdf. Accessed October 13, 2020.
3. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at www.nccn.org. Accessed October 13, 2020.
4. National Comprehensive Cancer Network. Breast Cancer Version 6.2020. Available at: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed October 13, 2020.
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6. National Comprehensive Cancer Network. Kidney Cancer Version 1.2021. Available at: http://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed October 13 , 2020.
7. National Comprehensive Cancer Network. Central Nervous System Cancers Version 3.2020. Available at: http://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed October 13, 2020.

8. Kidney Disease Improving Global Outcomes. KDIGO clinical practice guideline for the care of kidney transplant recipients. American Journal of Transplantation 2009; 9 (Suppl 3): Si- S155. doi: 10.1111/j.1600-6143.2009.02834.x
9. Bia M, Adey DB, Bloon RD, Chan L, Kulkarni S, and Tomlanovich S. KDOQI US Commentary on the 2009 KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Kidneys Dis 2010;56:189-218.
10. Lucey MR, Terrault N, Ojo L, et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transplantation 2013;19:3-26.
11. Costanzo MR, Dipchand A, Ross H, et al. The International Society of Heart and Lung Transplantation guidelines for the care of heart transplant recipients. Journal of Heart and Lung Transplantation. 2020; 29(8): 914-956.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Converted to new template. Approval durations lengthened to 6 and 12 months. For breast cancer, removed "Member is postmenopausal". Functional carcinoid tumors were moved to Section III as an indication for which coverage is NOT authorized.	07.17	08.17
1Q18 annual review: Removed dose form requirement by indication, no clinical difference expected (dosing is equivalent for SEGA indication). For RCC, per NCCN guidelines included list of first line therapies, added additional redirection to Cabometyx or Opdivo as this is a Category 1 preferred regimen over Afinitor for subsequent therapy. 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: Hodgkin's lymphoma, GIST, thymomas and thymic carcinomas, Waldenstrom's macroglobulinemia/ lymphoplasmacytic lymphoma, osteosarcoma, endometrial carcinoma.	11.09.17	02.18
Criteria added for new FDA indication: TSC-associated partial-onset seizures; specialist requirement added for all indications; references reviewed and updated.	05.22.18	08.18
1Q 2019 annual review: 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 - meningioma added, osteosarcoma removed, prior therapy added for DTC per NCCN; references reviewed and updated.	11.13.18	02.19
RT4: added new dosage form Zortress.	06.21.19	
1Q 2020 annual review: TSC association seizures - neurologist added; meningioma removed NCCN 2B; NET bronchopulmonary disease added NCCN 2A; added Medicaid line of business with 6/12 month approval durations; references reviewed and updated.	11.19.19	02.20
Added Appendix D with information regarding off-label use of Zortress in heart transplant; updated Appendix C to include Zortress.	07.01.20	
1Q 2021 annual review: oral oncology generic redirection language added; for HL, WM//LPL, thymoma, or thymic carcinoma, unresectable or disease not responding to previous therapy added; references reviewed and updated.	10.14.20	02.21

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of

medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.