

Clinical Policy Title:	everolimus
Policy Number:	RxA.8
Drug(s) Applied:	Afinitor®, Afinitor Disperz®, Zortress®
Original Policy Date:	02/07/2020
Last Review Date:	03/09/2021
Line of Business Policy Applies to:	All lines of business

Background

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

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, lymphangiomyomatosis	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

This clinical policy has been developed to authorize, modify, or determine coverage for individuals with similar conditions. Specific care and treatment may vary depending on individual need and benefits covered by the plan. This policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. This document may contain prescription brand name drugs that are trademarks of pharmaceutical manufacturers that are not affiliated with RxAdvance.

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 adult and pediatric patients aged 1 year and older 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)

Dosing Information			
Drug Name	Indication	Dosing Regimen	Maximum Dose
everolimus (Afinitor®)	Breast cancer, PNET (pancreas), NET (GI, lung), RCC, TSC-AML (renal)	10 mg PO once daily	20 mg/day
everolimus (Afinitor®/Afinitor Disperz®)	TSA-SEGA	4.5 mg/m ² PO once daily; adjust dose to attain trough concentrations of 5-15 ng/mL	Based on trough concentrations
everolimus (Afinitor Disperz®)	TSC-associated partial-onset seizures	5 mg/m ² PO once daily; adjust dose to attain trough	

		concentrations of 5-15 ng/mL	
everolimus (Zortress®)	Kidney transplant rejection prophylaxis	0.75 mg PO BID; adjust dose to attain trough concentrations of 3 to 8 ng/mL	
everolimus (Zortress®)	Liver transplant rejection prophylaxis	1 mg PO BID; adjust dose to attain trough concentrations of 3 to 8 ng/mL	

Dosage Forms

- everolimus (Afinitor®): Tablets: 2.5 mg, 5 mg, 7.5 mg and 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

Clinical Policy

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

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. Age ≥ 18 years;
4. Disease is HR-positive and HER2-negative;
5. Member is postmenopausal; or premenopausal receiving ovarian ablation or suppression;
6. Prior history of endocrine therapy (Appendix B) unless contraindicated or clinically significant adverse effects are experienced;
7. Prescribed in combination with exemestane, fulvestrant or tamoxifen;
8. Request is for Afinitor® or Afinitor Disperz®;
9. 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

Commercial: 6 months

Medicaid: 6 months

B. Neuroendocrine Tumors (must meet all):

1. Diagnosis of NET of one of the following origins (a – d):
 - a. Pancreatic;
 - b. GI tract;
 - c. Lung;
 - d. Bronchopulmonary (off-label);
 - e. Thymus (off-label);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is unresectable, locally advanced or metastatic;

5. Request is for Afinitor® or Afinitor Disperz®;
6. 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

Commercial: 6 months

Medicaid: 6 months

C. Renal cell carcinoma (must meet all):

1. Diagnosis of relapsed or stage IV (unresectable or metastatic) RCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. 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
5. Request is for Afinitor® or Afinitor Disperz®;
6. 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

Commercial: 6 months

Medicaid: 6 months

D. Renal Angiomyolipoma with Tuberous Sclerosis Complex (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. Age ≥ 18 years;
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

Commercial: 6 months

Medicaid: 6 months

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

1. Diagnosis of 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. 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

Commercial: 6 months

Medicaid: 6 months

F. Tuberos 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 or neurologist;
3. Request is for Afinitor Disperz®.

Approval duration

Commercial: 6 months

Medicaid: 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. Age ≥ 18 years;
4. For kidney transplant, failure of tacrolimus unless contraindicated or clinically significant adverse effects are experienced;
5. Request is for Zortress®;
6. 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: 6 months

Medicaid: 6 months

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

1. Diagnosis of one of the following (a, b, c, d, e, or f):
 - a. PEComa, angiomyolipoma (recurrent), or lymphangiomyomatosis;
 - b. Adult low-grade (WHO grade II) infiltrative supratentorial astrocytoma/oligodendroglioma;
 - c. Classical Hodgkin lymphoma (HL); WM//LPL (single agent therapy as alternative therapy for previously treated disease that does not respond to primary therapy or for progressive or relapsed disease);
 - d. Thyroid Carcinoma (HC, FC, PC), thymoma, or thymic carcinoma (refractory, recurrent, progressive or metastatic disease); Endometrial carcinoma (in combination with letrozole);
 - e. Gastrointestinal stromal tumors (GIST) (therapy in combination with imatinib, Sutent®, or Stivarga® for disease progression after single agent therapy with imatinib, Sutent®, and Stivarga®)*;

*Prior authorization may be required.

 - f. 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. Age 18 years or older;
4. Request is for Afinitor® or Afinitor Disperz®;
5. 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

Commercial: 6 months

Medicaid: 6 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all):

1. Member is currently receiving medication that has been authorized by RxAdvance or documentation supports that member is currently receiving Afinitor® or Afinitor Disperz® for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. 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: 12 months

Medicaid: 12 months

III. 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: Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma

HC: Hurthle cell carcinoma

FC: follicular carcinoma

PC: papillary Carcinoma

APPENDIX B: Therapeutic Alternatives

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

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 (fluoxyesterone) • 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
<i>GIST</i>		
imatinib (Gleevec®)	400 mg PO once daily or BID	800 mg/day
Sutent® (sunitinib)	50 mg PO once daily	50 mg/day
Stivarga® (regorafenib)	160 mg PO once daily	160 mg/day
<i>DTC</i>		
Lenvima® (lenvatinib)	24 mg PO once daily	24 mg/day
Nexavar® (sorafenib)	400 mg PO once daily	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® 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):**
 - Zortress®: malignancies and serious infections, kidney graft thrombosis, nephrotoxicity and mortality in heart transplantation.

APPENDIX D: General Information

- Advise patients of reproductive potential of the potential risk to a fetus and to use effective contraception.
- Avoid live vaccines.
- Afinitor®, Afinitor Disperz®: Complete recommended childhood vaccinations prior to starting treatment.

References

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6. National Comprehensive Cancer Network. Breast Cancer Version 1.2021. Available at: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed February 03, 2021.
7. 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. Accessed February 04, 2021
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9. 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. Accessed February 04, 2021.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy was established	01/2020	02/07/2020
2Q2020 P&T Review; Updates below, references reviewed and updated		
<ul style="list-style-type: none"> - TSC association seizures – neurologist added; - meningioma removed NCCN 2B; - NET bronchopulmonary disease added NCCN 2A; 	4/2020	05/20/2020

<ul style="list-style-type: none"> - specified max dose requirement in continued therapy applies to all diagnoses except partial-onset seizures associated with TSC and organ rejection prophylaxis; - Breast cancer: Added additional criteria of postmenopausal; or premenopausal receiving ovarian ablation or suppression. 		
<p>Policy was reviewed.</p> <ol style="list-style-type: none"> 1. Line of Business Policy Applies to was updated to “All lines of business”. 2. Initial therapy criteria I.H.1(a) & I.H.1(b) were added. 3. Continued therapy criteria II.A.1 was rephrased to “Currently receiving medication that has been authorized by Rxadvance...”. 4. Appendix B language updated to “Below are suggested therapeutic alternatives....”. 5. Appendix D was updated. 6. References were reviewed and updated. 	<p>02/11/2021</p>	<p>03/09/2021</p>