Clinical Policy Title:	everolimus
Policy Number:	RxA.008
Drug(s) Applied:	Afinitor®, Afinitor Disperz®, Zortress®
Original Policy Date:	02/07/2020
Last Review Date:	10/19/2022
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	---
Pancreatic neuroendocrine tumor (PNET)	X - adults	X - adults per NCCN	---
Neuroendocrine tumors (NET) Gastrointestinal (GI), lung, thymic-*off-label*)	X - adults	X - adults per NCCN	---
Renal cell carcinoma (RCC)	X - adults	X - adults per NCCN	---
Tuberous sclerosis complex-angiomyolipoma (TSC-AML (renal))	X - adults	X - adults per NCCN	---
Tuberous sclerosis complex-subepndymal giant cell astrocytoma (TSC-SEGA)	X - 1 year and older	X - 1 year and older	---
Tuberous sclerosis complex-seizures (TSC-seizures)	---	X - 2 years and older	---
Prophylaxis of organ rejection	---	---	X - adults
Recommended NCCN uses (adults)			
Meningioma	X	X	---
Hodgkin lymphoma (HL)	X	X	---
soft tissue sarcoma-gastrointestinal stromal tumor (STS-GIST)	X	X	---
soft tissue sarcoma-perivascular epithelioid cell tumor (STS-PEComa), angiomyolipoma, lymphangioleiomyomatosis	X	X	---
Thymoma/thymic carcinoma	X	X	---

Differentiated thyroid carcinoma (DTC)	X	X	---
Waldenstrom macroglobulinemia/ lymphoplasmacytic lymphoma (WM/LPL)	X	X	---
Endometrial carcinoma	X	X	---
Histiocytic neoplasms	X	X	---

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.
- 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.

Limitation(s) of use:

- Afinitor® is not indicated for the treatment of patients with functional carcinoid tumors.

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 orally once daily Mild hepatic impairment (Child-Pugh class A)- 7.5 mg orally	10 mg/day

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
		once daily; decrease the dose to 5 mg orally once daily if a dose of 7.5 mg once daily is not tolerated. Moderate hepatic impairment (Child-Pugh class B)- 5 mg orally once daily; decrease the dose to 2.5 mg orally once daily if a dose of 5 mg once daily is not tolerated. Severe hepatic impairment (Child-Pugh class C)- 2.5 mg orally once daily if the desired benefit outweighs the risk; do not exceed a dose of 2.5 mg once daily.	
everolimus (Afinitor®/Afinitor Disperz®)	TSA-SEGA	4.5 mg/m^2 orally once daily; adjust dose to attain trough concentrations of 5-15 ng/mL Severe hepatic impairment (Child-Pugh class C)- 2.5 mg/m^2 orally once daily.	Based on trough concentrations
everolimus (Afinitor Disperz®)	TSC-associated partial-onset seizures	5 mg/m^2 orally once daily; adjust dose to attain trough concentrations of 5-15 ng/mL Severe hepatic impairment (Child-Pugh class C)- 2.5 mg/m^2 orally once daily.	
everolimus (Zortress®)	Kidney transplant rejection prophylaxis	0.75 mg orally twice daily; adjust dose to attain trough concentrations of 3 to 8 ng/mL	
everolimus (Zortress®)	Liver transplant rejection prophylaxis	1 mg orally twice daily; adjust dose to attain trough concentrations of 3 to 8 ng/mL Mild Hepatic Impairment: Reduce initial daily dose by one-third Moderate or Severe Hepatic Impairment: Reduce initial daily dose by one-half	

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. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

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).

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

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 – e):
   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).

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

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 (e.g. Inlyta®, Votrient®, Sutent®, Nexavar®) 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).
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

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

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. Age ≥ 1 years;
4. Member is not a candidate for curative surgical resection;
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).
   *Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval duration

Commercial: 6 months
Medicaid: 6 months

F. Tuberous Sclerosis Complex-Associated Partial-Onset Seizures (must meet all):
1. Diagnosis of partial-onset seizures associated with TSC;
2. Age ≥ 2 years;
3. Prescribed by or in consultation with an oncologist or a neurologist;
4. 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, f, g, h, I and j):
   a. Soft Tissue Sarcoma- PEComa, angiomyolipoma (recurrent), or lymphangioleiomyomatosis;
   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;
   g. Histiocytic Neoplasms (Langerhans Cell Histiocytosis, Rosai-Dorfman Disease, a Erdheim-Chester Disease
   h. Uterine Neoplasms - Endometrial Carcinoma
   i. Waldenström Macroglobulinemia / Lymphoplasmacytic Lymphoma - Waldenström Macroglobulinemia / Lymphoplasmacytic Lymphoma
   *Prior authorization may be required.
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;

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 10 mg 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: subepndymal 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	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® • sunitinib (Sutent®) • Opdivo® ± Yervoy® • bevacizumab (Avastin®) ± (Intron A, Tarceva® or everolimus (Afinitor®/Afinitor Disperz®)) • Proleukin® • Cabometyx® • temsirolimus (Torisel®) • Inlyta® • everolimus (Afinitor®/Afinitor Disperz®) ± Lenvima • Nexavar® • Tarceva® (erlotinib)	Varies	Varies
GIST		
imatinib (Gleevec®)	400 mg orally once daily or twice daily	800 mg/day
sunitinib (Sutent®)	50 mg orally once daily	87.5 mg/day
Stivarga®	160 mg orally once daily	160 mg/day
DTC		
Lenvima®	24 mg orally once daily	24 mg/day
sorafenib tosylate (Nexavar®)	400 mg orally twice daily	800 mg/day

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

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.

*Contraindications listed reflect direct statements made in manufacturer's package insert; for additional uses, warnings, and precautions, please refer to clinical guidelines.

- 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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4. National Comprehensive Cancer Network. Kidney Cancer Version 1.2023. Available at: http://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf . Accessed July 07, 2022.
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6. National Comprehensive Cancer Network. Breast Cancer Version 4.2022. Available at: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed July 07, 2022.
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. Available at: https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2009-Transplant-Recipient-Guideline-English.pdf. Accessed July 07, 2022.
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10. Clinical Pharmacology [database online] powered by Clinical Key. Tampa, FL: Elsevier, 2022. Accessed with subscription at: http://www.clinicalkey.com. Accessed July 07, 2022.

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 - TSC association seizures – neurologist added; - meningioma removed NCCN 2B; - NET bronchopulmonary disease added NCCN 2A; - 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.	4/2020	05/20/2020
Policy was reviewed. 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.	02/11/2021	03/09/2021
Policy was reviewed. 1. Dosing Information, Maximum Dose, Afinitor®: Updated to maximum dosing information from 20 mg/day to 10 mg/day for indication Breast cancer, PNET (pancreas), NET (GI, lung), RCC, TSC-AML (renal). 2. Dosing Information, Dosing Regimen, Afinitor®: Updated to include hepatic impairment dosing information for indication Breast cancer, PNET (pancreas), NET (GI, lung), RCC, TSC-AML (renal), TSA-SEGA. 3. Dosing Information, Dosing Regimen, Afinitor Disperz®: Updated to include hepatic impairment dosing information for TSA-SEGA and TSC-associated partial- onset seizures. 4. Dosing Information, Dosing Regimen Zortress®: Updated to include hepatic impairment dosing information for Liver transplant rejection prophylaxis. 5. Statement about provider sample ''The provision of provider samples does not	12/06/2021	01/17/2022

guarantee coverage…" was added to Clinical Policy.

6. Initial Approval Criteria
   a. IE3: Updated to include new age criteria Age ≥ 1 years.
   b. IF2: Updated to include new age criteria Age ≥ 2 years
7. Initial Approval Criteria, IH1: Updated to include new indication
   a. Histiocytic Neoplasms (Langerhans Cell Histiocytosis, Rosai-Dorfman Disease, a Erdheim-Chester Disease
   b. Uterine Neoplasms - Endometrial Carcinoma
   c. Waldenström Macroglobulinemia / Lymphoplasmacytic Lymphoma - Waldenström Macroglobulinemia / Lymphoplasmacytic Lymphoma
8. Appendix B, Drug Name: Updated to remove unavailable generic therapeutic alternative
   a. lenvatinib
   b. regorafenib
   c. pazopanib
   d. nivolumab
   e. iplimumab tamoxifen
   f. interferon alfa-2b
   g. aldesleukin
   h. cabozantinib
   i. axitinib
   j. sorafenib
9. Appendix B, Maximum Dose,
   a. sunitinib (Sutent®):Updated maximum dose information from 50 mg/day to 87.5 mg/day for indication GIST.
   b. Nexavar :Updated maximum dose information from 400 mg/day to 800 mg/day for indication DTC.
10. Therapeutic Alternatives was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance..".
11. Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only".
12. Disclaimer about contraindications," Contraindications listed reflect statements

made in the manufacturer's package insert.." was added to Appendix C. 13. References were reviewed and updated.		
Policy was reviewed. 1. Continued Therapy Criteria II.A.3.a: Updated new dose does not exceed from 20 mg to 10 mg per day. 2. Appendix B, Drug Name: Updated to include generic therapeutic alternative sorafenib tosylate. 3. References were reviewed and updated.	07/04/2022	10/19/2022