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

Reference Number: CP.PHAR.63
Effective Date: 06.01.11
Last Review Date: 05.22
Line of Business: Commercial, HIM*, Medicaid

Coding Implications
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.

**For Health Insurance Marketplace (HIM),* *Afinitor Disperz is non-formulary and should not be approved using these criteria; refer to the formulary exception policy, HIM.PA.103.*

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	---
Histiocytic neoplasms	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.*
- 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 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: Afinitor is not indicated for the treatment of patients with functional carcinoid tumors.*

† 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.

It is the policy of health plans affiliated with Centene Corporation® 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. Disease is HR-positive and HER2-negative;
6. History of endocrine therapy (*see Appendix B*) unless contraindicated or clinically significant adverse effects are experienced;
7. For Afinitor or Afinitor Disperz requests, member must use everolimus, if available, 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:
Medicaid – 6 months
HIM – 6 months *(refer to HIM.PA.103 for Afinitor Disperz)*
Commercial – 12 months or duration of request, whichever is less
Legacy Wellcare – 12 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 – d):
   a. Pancreatic;
   b. GI tract;
   c. Lung;
   d. Bronchopulmonary (off-label);
   e. Thymus (off-label);
3. Disease is unresectable, locally advanced or metastatic;
4. Prescribed by or in consultation with an oncologist;
5. Age ≥ 18 years;
6. For Afinitor or Afinitor Disperz requests, member must use everolimus, if available, unless contraindicated or clinically significant adverse effects are experienced;
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:
Medicaid – 6 months
HIM – 6 months *(refer to HIM.PA.103 for Afinitor Disperz)*
Commercial – 12 months or duration of request, whichever is less
Legacy Wellcare – 12 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) RCC;
3. Prescribed by or in consultation with an oncologist;

4. Age ≥ 18 years;
5. For Afinitor or Afinitor Disperz requests, member must use everolimus, if available, unless contraindicated or clinically significant adverse effects are experienced;
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:
Medicaid – 6 months
HIM – 6 months *(refer to HIM.PA.103 for Afinitor Disperz)*
Commercial – 12 months or duration of request, whichever is less
Legacy Wellcare – 12 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 requests, member must use everolimus, if available, unless contraindicated or clinically significant adverse effects are experienced;
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:
Medicaid – 6 months
HIM – 6 months *(refer to HIM.PA.103 for Afinitor Disperz)*
Commercial – 12 months or duration of request, whichever is less
Legacy Wellcare – 12 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. Member is not a candidate for curative surgical resection.
5. For Afinitor or Afinitor Disperz requests, member must use everolimus, if available, unless contraindicated or clinically significant adverse effects are experienced;

Approval duration:

Medicaid – 6 months
HIM – 6 months *(refer to HIM.PA.103 for Afinitor Disperz)*
Commercial – 12 months or duration of request, whichever is less
Legacy Wellcare – 12 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. Prescribed by or in consultation with an oncologist or neurologist;
4. For Afinitor Disperz requests, member must use everolimus, if available, unless contraindicated or clinically significant adverse effects are experienced.

Approval duration:
Medicaid – 6 months
HIM – *refer to HIM.PA.103*
Commercial – 12 months or duration of request, whichever is less
Legacy Wellcare – 12 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 kidney transplant, failure of tacrolimus unless contraindicated or clinically significant adverse effects are experienced;
6. For Zortress requests, member must use everolimus, if available, 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:
Medicaid/HIM/Commercial: 6 months
Legacy Wellcare – 12 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-f):
   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*
f. Histiocytic neoplasms (i.e., Erdheim-Chester disease, Langerhans cell histiocytosis, Rosai-Dorfman disease);

3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. For Afinitor or Afinitor Disperz requests, member must use everolimus, if available, unless contraindicated or clinically significant adverse effects are experienced;
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:
Medicaid – 6 months
HIM – 6 months *(refer to HIM.PA.103 for Afinitor Disperz)*
Commercial – 12 months or duration of request, whichever is less
Legacy Wellcare – 12 months

I. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy
A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via Centene benefit, 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 Afinitor, Afinitor Disperz, Zortress requests, member must use everolimus, if available, unless contraindicated or clinically significant adverse effects are experienced;

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:
Medicaid – 12 months
HIM – 12 months *(refer to HIM.PA.103 for Afinitor Disperz)*
Commercial – 12 months or duration of request, whichever is less
Legacy Wellcare – 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid 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 with clear cell histology per NCCN		
• Votrient® (pazopanib) • Sutent® (sunitinib) • Opdivo® (nivolumab) ± Yervoy® (iplimumab) • 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	
Kidney transplant rejection prophylaxis	Zortress 0.75 mg PO BID; adjust dose to attain trough concentrations of 3 to 8 ng/mL	
Liver transplant rejection prophylaxis	Zortress 1 mg PO BID; adjust dose to attain trough concentrations of 3 to 8 ng/mL	

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; April 2021. Available at: https://www.novartis.us/sites/www.novartis.us/files/afinitor.pdf. Accessed November 13, 2021.
2. Zortress Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; January 2021. Available at: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/zortress.pdf. Accessed November 13, 2021.
3. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at www.nccn.org. Accessed November 13, 2021.
4. National Comprehensive Cancer Network. Breast Cancer Version 8.2021. Available at: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed November 13, 2021.
5. National Comprehensive Cancer Network. Neuroendocrine and Adrenal Tumors Version 3.2021. Available at: http://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed November 13, 2021.
6. National Comprehensive Cancer Network. Kidney Cancer Version 3.2022. Available at: http://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed November 13, 2021.
7. National Comprehensive Cancer Network. Central Nervous System Cancers Version 2.2021. Available at: http://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed November 13, 2021.
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. Breda A, Budde K, Figueiredo KA, et al. Renal Transplantation Guidelines 2019. European Association of Urology (EAU). Available at: http://www.uroweb.org/guideline/renal-transplantation/.
11. 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.
12. 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.

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	P&T Approval Date
Added thyroid carcinoma as an NCCN compendium supported use.	06.14.17	11.17
1Q18 annual review: Combined Medicaid and Commercial policies; 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.	11.09.17	02.18
Criteria added for new FDA indication: TSC-associated partial-onset seizures; references reviewed and updated.	05.22.18	08.18
Zortress added to the policy; added HIM line of business; added that requested agent is for each FDA-approved agent for that indication; references reviewed and updated.	09.04.18	11.18
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 - 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 of Zortress 1 mg.	06.21.19	
1Q 2020 annual review: 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; 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 clarify Zortress's boxed warning in heart transplant.	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 to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	10.14.20	02.21

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2022 annual review: added histiocytic neoplasms indication per NCCN; added legacy WellCare auth durations (WCG.CP.PHAR.63 to retire); clarified oral oncology generic redirection language to "must use"; references reviewed and updated.	11.13.21	02.22
Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less	01.20.22	05.22
Template changes applied to other diagnoses/indications and continued therapy section.	11.23.22	

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to

recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.