BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

AFINITOR® (everolimus) tablet
AFINITOR® DISPERZ (everolimus) tablet for suspension
Everolimus tablet
Everolimus tablet for suspension
TORPENZ™ (everolimus) tablet

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

- **Criteria for initial therapy:** Afinitor (everolimus) tablet, Afinitor Disperz (everolimus) tablet for suspension, Torpenz (everolimus) tablet, everolimus tablet, everolimus tablet for suspension are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist, Nephrologist, Gastroenterologist, Neurologist, or Gynecologist depending upon indication or use

2. Individual has a confirmed diagnosis of **ONE** of the following:
    a. **For Afinitor tablet and everolimus tablet:**
        i. Postmenopausal woman with advanced hormone receptor positive, HER2-negative breast cancer used in combination with exemestane, after failure of treatment with letrozole or anastrozole
        ii. Individual 18 years of age or older with progressive neuroendocrine tumors of pancreatic origin (PNET) with unresectable, locally advanced or metastatic disease (Individual does not have functional carcinoid tumor)
        iii. Individual 18 years of age or older with progressive, well-differentiated, nonfunctional NET of gastrointestinal (GI) or lung origin with unresectable, locally advanced or metastatic disease (Individual does not have functional carcinoid tumor)
        iv. Individual 18 years of age or older with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib
        v. Individual 18 years of age or older with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery
        vi. Individual 1 years of age or older with TSC who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected
        vii. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

    b. **For Afinitor Disperz tablet for suspension and everolimus tablet for suspension:**
        i. Individual 1 year of age or older with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected
        ii. Individual 2 years of age or older who have TSC associated partial-onset seizures used as adjuvant treatment
        iii. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

    c. **For Torpenz tablet:**
        i. Postmenopausal woman with advanced hormone receptor positive, HER2-negative breast cancer used in combination with exemestane, after failure of treatment with letrozole or anastrozole
        ii. Individual 18 years of age or older with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery
        iii. Individual 1 years of age or older with TSC who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected
        iv. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

3. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Lipid profile
    b. Fasting serum glucose
    c. Negative pregnancy test is a woman of childbearing potential
    d. Eastern Co-operative Oncology Group (ECOG) Performance Status 0-2

4. **For Afinitor tablet and Torpenz tablet**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic everolimus tablet** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. **For Afinitor Disperz tablet for suspension**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic everolimus tablet for suspension** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. The individual does **NOT** have the FDA-label contraindication of hypersensitivity to other rapamycin derivatives (e.g., Torisel (temsirolimus), Rapamune (sirolimus))

7. Afinitor tablet, Torpenz tablet, or everolimus tablet and Afinitor Disperz tablet for suspension, or everolimus tablet for suspension will not be used in combination

8. Tablet formulations will not be used interchangeably with tablet for suspension formulations

9. Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation such as:
    a. Use of live vaccines
    b. Concomitant use of P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, others)
    c. Concomitant use of ACE inhibitors (e.g., enalapril, lisinopril, others)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Afinitor (everolimus) tablet, Afinitor Disperz tablet for suspension (everolimus), Torpenz (everolimus) tablet, everolimus tablet, everolimus tablet for suspension are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist, Nephrologist, Gastroenterologist, Neurologist, or Gynecologist depending upon indication or use

2. Individual's condition has responded while on therapy with response defined as there is no evidence of disease progression or unacceptable toxicity

3. Individual has been adherent with the medication

4. **For Afinitor tablet and Torpenz tablet**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic everolimus tablet** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. **For Afinitor Disperz tablet for suspension**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic everolimus tablet for suspension** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use as follows:
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effects such as:
        i. Life-threatening non-infectious pneumonitis that has not recovered or has recurred and needs urgent intervention
        ii. Invasive fungal infection needing antifungal treatment
        iii. Life-threatening stomatitis needing urgent intervention
        iv. Life-threatening febrile neutropenia needing urgent intervention
        v. Myelosuppression
        vi. Life-threatening hyperglycemia or dyslipidemia
        vii. Life-threatening non-hematologic toxicity or serious non-hematologic toxicity that recurs after dose reduction
        viii. Clinically significant hypersensitivity reactions
        ix. Angioedema

7. Afinitor tablet, Torpenz tablet, or everolimus tablet and Afinitor Disperz tablet for suspension or everolimus tablet for suspension will not be used in combination

8. Tablet formulations will not be used interchangeably with tablet for suspension formulations

9. Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation such as:
    a. Use of live vaccines
    b. Concomitant use of P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, others)
    c. Concomitant use of ACE inhibitors (e.g., enalapril, lisinopril, others)

Renewal duration: 12 months

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- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of Non-Cancer Medications**

  2. **Off-Label Use of Cancer Medications**

Description:

Afinitor (everolimus) is indicated for the treatment of postmenopausal women with advanced hormone receptor positive, HER2-negative breast cancer (advanced HR+ BC) used in combination with exemestane, after failure of treatment with letrozole or anastrozole; for the treatment of adult patients with progressive neuroendocrine tumors of pancreatic origin (PNET) with unresectable, locally advanced or metastatic disease and treatment of adult patients with progressive, well-differentiated, nonfunctional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin with unresectable, locally advanced or metastatic disease (everolimus is not indicated for the treatment of patients with functional carcinoid tumors); for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib; and for the treatment of adult patients with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery.

Afinitor (everolimus tab) and Afinitor Disperz (everolimus tab for suspension) are indicated for the treatment of pediatric (1 year of age or older) and adult patients with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.

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

Torpenz (everolimus tab) is indicated for the treatment of postmenopausal women with advanced hormone receptor positive, HER2-negative breast cancer (advanced HR+ BC) used in combination with exemestane, after failure of treatment with letrozole or anastrozole; for the treatment of adult patients with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery; and for the treatment of pediatric (1 year of age or older) and adult patients with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.

Everolimus is an inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers. Everolimus binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation with mTOR complex 1 (mTORC1) and thus inhibition of mTOR kinase activity. Inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in *in vitro* and/or *in vivo* studies.

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Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

ECOG Performance status: (also known as WHO performance status and Zubrod performance status)

Eastern Co-operative Oncology Group (ECOG) Performance Status	
Grade	ECOG description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982	

NCCN recommendation definitions:

Category 1:
Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A:
Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B:
Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3:
Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

Resources:

Afinitor (everolimus) tablet and Afinitor Disperz (everolimus) tablet for oral suspension product information, revised by Novartis Pharmaceuticals Corporation 02-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 03, 2024.

Everolimus tablet product information, revised by Mylan Pharmaceuticals Inc. 10-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 03, 2025.

Everolimus tablet for oral suspension product information, revised by Mylan Pharmaceuticals Inc. 05-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 03, 2024.

Torpenz (everolimus) tablet product information, revised by Upsher-Smith Laboratories, LLC 03-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 03, 2024.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Breast Cancer Version 1.2025 –Updated January 31, 2025. Available at https://www.nccn.org. Accessed February 03, 2025.

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Everolimus tablet
Everolimus tablet for suspension
TORPENZ™ (everolimus) tablet

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Central Nervous System Cancers Version 4.2024 –Updated January 21, 2025. Available at https://www.nccn.org. Accessed February 03, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Kidney Cancer Version 3.2025 –Updated January 09, 2025. Available at https://www.nccn.org. Accessed February 03, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Neuroendocrine and Adrenal Tumors Version 4.2024 –Updated January 17, 2025. Available at https://www.nccn.org. Accessed February 03, 2025.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.