DRUG DETERMINATION POLICY

Title: DDP-14 Afinitor

Effective Date: 06/12/2019

Physicians Health Plan
PHP Insurance Company
PHP Service Company

Important Information - Please Read Before Using This Policy

The following policy applies to health benefit plans administered by PHP and may not be covered by all PHP plans. Please refer to the member's benefit document for specific coverage information. If there is a difference between this general information and the member's benefit document, the member's benefit document will be used to determine coverage. For example, a member's benefit document may contain a specific exclusion related to a topic addressed in a coverage policy.

Benefit determinations for individual requests require consideration of:

1. The terms of the applicable benefit document in effect on the date of service.
2. Any applicable laws and regulations.
3. Any relevant collateral source materials including coverage policies.
4. The specific facts of the particular situation.

Contact PHP Customer Service to discuss plan benefits more specifically.

1.0 Policy:

This policy describes the determination process for coverage of specific drugs.

This policy does not guarantee or approve Benefits. Coverage depends on the specific Benefit plan. Pharmacy Benefit Determination Policies are not recommendations for treatment and should not be used as treatment guidelines.

2.0 Background or Purpose:

Afinitor (everolimus) is a specialty drug indicated for a number of diagnoses and is associated with significant toxicity. These criteria were developed and implemented to ensure appropriate use for the intended diagnoses and mitigation of toxicity, if possible.

3.0 Clinical Determination Guidelines:

A. Neuroendocrine Tumors
    1. Diagnosis and severity:
        a. Progressive, unresectable, locally advanced or metastatic disease (one below):
            i. Pancreatic neuroendocrine tumors (PNET).
            ii. Well-differentiated, nonfunctional GI or lung neuro-endocrine tumors.
    2. Other therapies: none.
    3. Dosage regimen: Afinitor (everolimus): 10 mg once daily.
    4. Approval.
        a. Initial: six months.
        b. Re-approval: six months until disease progression or unacceptable toxicity.

B. Breast Cancer
    1. Diagnosis and severity (all below):
        a. Postmenopausal.

b. Advanced HR+ disease.

c. HER2-negative.

2. Other therapies: contraindicated, failed or had significant adverse effects.

a. Femora (letrozole).

b. Arimidex (anastrozole).

3. Dosage regimen (everolimus).

a. 10 mg once daily.

b. Combination with Aromasin (exemestane).

4. Approval.

a. Initial: six months.

b. Re-approval: six months until disease progression or unacceptable toxicity.

C. Renal Cell Carcinoma (RCC), advanced

1. Diagnosis and severity:

a. Advanced RCC with predominant clear cell histology.

b. Relapsed or medically unresectable RCC with non-clear cell histology.

2. Other therapies: contraindicated, failed or had significant adverse effects (1 below):

a. Listed in FDA approved indication: Sutent (sunitinib) or Nexavar (sorafenib); OR

b. Not listed in indication: Votrient (pazopanib) or Inlyta (axltinib).

3. Dosage regimen Afinitor (everolimus): 10 mg once daily.

4. Approval.

a. Initial: six months.

b. Re-approval: six months until disease progression or unacceptable toxicity.

D. Tuberous Sclerosis Complex-associated Partial Onset Seizures

1. Age: $\geq$2 years

2. Diagnosis and severity: inadequate control of partial seizures (at least two seizures per week)

3. Other Therapies: contraindication, failure or significant adverse effects to at least two formulary anti-epileptic drugs.

4. Dosage regimen (everolimus): 5mg/m^2 once daily.

5. Approval.

a. Initial: six months.

b. Re-approval: six months until disease progression or unacceptable toxicity.

E. Tuberous Sclerosis Complex-associated Renal Angiomyolipoma (AML)

1. Diagnosis and severity (both below):

a. Tuberous sclerosis complex (TSC); AND

b. AML.

2. Other therapies: contraindicated, failed or had significant adverse effects.

a. Surgery: AMLs greater than 4cm; symptoms refractory to conservative measures; high suspicion of malignancy.

3. Radiofrequency ablation and cryo-ablation: AMLs less than 4 cm.
4. Dosage regimen for Afinitor (everolimus): 10 mg once daily.
5. Approval.
    a. Initial: six months.
    b. Re-approval: six months until disease progression or unacceptable toxicity.

F. Tuberous Sclerosis complex-associated Sub-ependymal Giant Cell Astrocytoma (SEGA)
1. Diagnosis and severity (both below):
    a. Tuberous sclerosis complex (TSC); AND
    b. SGCT needs intervention and not curably resectable or symptomatic/growing after surgery.
2. Other therapies: surgery if advisable.
3. Dosage regimen:
    a. Initial: Afinitor (everolimus): 4.5 mg/m^2 once daily
    b. Adjustment: Trough less than 5 mg/mL- increase 2 to 2.5 mg/day; greater than 5 mg/mL - decrease 2 to 2.5 mg/day (at lowest dose give every other day).
4. Approval.
    a. Initial: six months.
    b. Re-approval: six months until disease progression or unacceptable toxicity.

4.0 Unique Configuration/Prior Approval/Coverage Details:

None.

5.0 References, Citations & Resources:

1. Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Afinitor, accessed June 2019.
2. Metastatic well-differentiated pancreatic neuroendocrine tumors: Systemic therapy options to control tumor growth and symptoms of hormone hypersecretion. UpToDate [internet] Accessed April 2016.
3. Available from: http://www.uptodate.com /contents/metastatic-well-differentiated-pancreatic-neuroendocrine.
5. Tuberous Sclerosis complex: Management. UpToDate [internet] Accessed April 2016. Available from: http://www.uptodate.com /contents/tuberous-sclerosis-complex-management.
5. Renal manifestations of tuberous sclerosis complex. UpToDate [internet] Accessed April 2016. Available from: http://www.uptodate.com /contents/renal-manifestations-of-tuberous-sclerosis-complex.
6. Long-term everolimus treatment in individuals with tuberous sclerosis complex: a review of current literature. 2015. Pediatric Neurology: 53;23-30.

6.0 Appendices:

Appendix I: Patient Safety and Monitoring

Drug	Adverse Reactions	Monitoring	REMS
Afinitor everolimus	• CV: edema (13-39%), HTN (4-13%) • CNS: malaise (≤45%), fatigue (14-44%), HA (19-29%), migraine (≤30%), behavioral problems (21%), insomnia (6-14%), dizziness (7-12%) • Derm: skin rash (21-59%), cellulitis (29%), acne (10-22%), nail dx (5-22%), pruritus 13-20%), xeroderma (13%) • Endo/metab: ↑cholesterol (81-85%), ↓ Na bicarb (56%), ↑ tri-glycerides (27-52%), ↑PO3 (9-49%), ↓Ca (37%), ↓ albumin (13-33%), ↑ glucose (14-25%), amenorrhea (15-17%) • GI: stomatitis (62-78%), diarrhea (14-50%), abdominal pain (9-36%), ↓ appetite (6-30%), N/V (15-29%), weight loss (9-28%), anorexia (25%), dysgeusia 5-22%), mucositis (19%), constipation (10-14%), xerostomia (8-11%) • GU: UTI (5-16%), irregular menses (10-11%) • Hem/Onc: ↑ PPT, anemia (41-61%), ↓ LYMP (45-54%), ↓plts (45-54%), neutropenia (46%), leukopenia (37%) • Hep: ↑ alk phos. (32-74%), ↑ AST (23-69%), ↑ALT (48-51%) • MSK: weakness (13-33%), arthralgia (13-20%), back/limb pain (8-15%) • Resp: resp tract inf. (31%), cough (20-30%), rhinitis (25%), nasopharyngitis (6-25%), URI (5-11%), dyspnea (20-24%), epistaxis (5-22%), pneumonitis (1-19%), oral pain (11%) • Misc: fever (15-31%), infection (37-50%) • Preg category: C	• Labs (prior & during): CBC w diff.); LFT, Cr, Urinary protein & BUN; serum glucose & lipid profile. • HEM/Onc: monitor for S & Sx of malignancy • Infection: monitor for S & Sx • Resp: monitor S & Sx of non-infectious pneumonitis	None Needed

7.0 Revision History:

Original Effective Date: 06/30/2016

Last Approval Date: 06/12/2019

Next Review Date: 06/12/2020

Revision Date	**Reason for Revision**
March 2019	Transfer to new format
April 2019	Presented and approved at P & T Workgroup and Committee