POLICY NUMBER UM ONC_1192	SUBJECT Afinitor™ (everolimus)		DEPT/PROGRAM UM Dept	PAGE 1 OF 5
DATES COMMITTEE REVIEWED 01/04/12, 04/11/12, 12/12/12, 01/02/13, 01/03/14, 06/09/15, 04/12/16, 02/06/17, 01/02/17, 01/10/18, 01/08/19, 12/11/19, 01/08/20	APPROVAL DATE January 8, 2020	EFFECTIVE DATE January 8, 2020	COMMITTEE APPROVAL DATES (latest version listed last) 01/04/12, 04/11/12, 12/12/12, 01/02/13, 01/03/14, 06/09/15, 04/12/16, 02/06/17, 01/02/17, 01/10/18, 01/08/19, 12/11/19, 01/08/20	
PRIMARY BUSINESS OWNER: UM APPROVED BY: Dr. Andrew Hertler		COMMITTEE/BOARD APPROVAL Utilization Management Committee		
URAC STANDARDS HUM 1	NCQA STANDARDS UM 2		ADDITIONAL AREAS OF IMPACT	
CMS REQUIREMENTS	STATE/FEDERAL REQUIREMENTS		APPLICABLE LINES OF BUSINESS All	

I. PURPOSE

To define and describe the accepted indications for Afinitor (everolimus) usage in the treatment of cancer.

II. DEFINITIONS

Afinitor (everolimus): an intracellular protein and inhibits the mammalian target of rapamycin (mTOR) kinase downstream signaling involved in cell proliferation and survival. Everolimus forms a complex with the cytoplasmic FK506 Binding protein 12 (FKBP-12) and the everolimus: FKBP-12 complex binds to and inhibits the mammalian Target of Rapamycin (mTOR) and phosphorylates P70 S6 ribosomal protein kinase (a substrate of mTOR). The phosphorylation of P70 S6 ribosomal protein kinase by the everolimus complex prevents protein synthesis and cell proliferation.

Afinitor (everolimus) is FDA approved for the treatment of advanced neuroendocrine tumors of pancreatic origin, advanced renal cell carcinoma, asubependymal giant cell astrocytoma, and advanced breast cancer.

Non-FDA approved indication include: Waldenström's macroglobulinemia/Lymphoplasmacytic lymphoma and lung neuroendocrine tumors

Afinitor (everolimus) is available as 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets.

III. POLICY

New Century is responsible for processing all medication requests from network ordering providers. Medications not authorized by New Century may be deemed as not approvable and therefore not reimbursable.

Treatment request outside the approved FDA manufacturer labeling or CMS approved compendia must follow CMS Medicare Benefit Policy Manual Chapter 15. If references are not produced, delays may occur to the processing of such request.

Inclusion Criteria: Afinitor (everolimus) may be considered medically necessary when any of the following selection criteria is met:

1. **PREFERRED MEDICATION GUIDANCE FOR INITIAL REQUEST:**
    a. When health plan Medicaid coverage provisions- including any applicable PDLs (Preferred Drug Lists)- conflict with the coverage provisions in this drug policy, health plan Medicaid coverage provisions take precedence per the **Preferred Drug Guidelines OR**

b. When health plan Exchange coverage provisions- including any applicable PDLs (Preferred Drug Lists)- conflict with the coverage provisions in this drug policy, health plan Exchange coverage provisions take precedence per the **Preferred Drug Guidelines OR**

c. For Health Plans that utilize NCH UM Oncology Clinical Policies as the initial clinical criteria, the **Preferred Drug Guidelines shall follow NCH L1 Pathways** when applicable, otherwise shall follow NCH drug policies: http://pathways.newcenturyhealth.com **AND**

d. Continuation requests of previously approved non-preferred medication are not subject to this provision **AND**

e. When available, generic alternatives are preferred over brand-name drugs.

2. **Breast Cancer**

    a. Subsequent therapy in combination with exemestane, fulvestrant, or tamoxifen for hormone receptor-positive, human epidermal growth factor receptor 2-negative in post-menopausal women with recurrent or metastatic disease previously treated with a nonsteroidal aromatase inhibitor or tamoxifen.

3. **Renal Cell Carcinoma (RCC)**

    a. Subsequent therapy as a single agent OR in combination with lenvatinib/bevacizumab for relapsed or medically unresectable stage IV disease in members who have progressed on prior tyrosine kinase inhibitor, including Sutent (sunitinib), Nexavar (sorafenib), or Votrient (pazopanib) therapy.

4. **Advanced Neuroendocrine Tumors of Pancreatic Origin**

    a. Everolimus is indicated for the treatment of progressive neuroendocrine tumors of pancreatic origin in members with unresectable locally advanced or metastatic disease.

5. **Lung Neuroendocrine tumor**

    a. Used as treatment for stage IIIb-IV or unresectable low- or intermediate-grade neuroendocrine carcinoma.

6. **Waldenström's macroglobulinemia/Lymphoplasmacytic lymphoma**

    a. Single-agent salvage therapy for disease that does not respond to primary therapy or for progressive or relapsed disease.

7. **Hodgkin Lymphoma**

    a. Used subsequent therapy as a single agent for refractory or relapsed disease.

8. **Neuroendocrine Tumors of the GI tract, Lung, and Thymus**

    a. Used in locoreginal unresectable or metastatic progressive disease.

9. **Soft Tissue Sarcoma – PEComa/Recurrent Angiomyolipoma/Lymphangioleiomyomatosis**

    a. Used in combination with either imatinib, sunitinib, or regorafenib for disease progression after single-agent therapy with imatinib, sunitinib, and regorafenib.

10. **Thymomas and Thymic Carcinomas**

    a. Used as single agent in second-line therapy.

Exclusion Criteria: Afinitor (everolimus) is not considered medically necessary when any of the following selection criteria is met:

1. The member has stage I-III RCC OR has not progressed on a TKI, including Nexavarr (sorafenib), Sutent (sunitinib), or Votrient (pazopanib).
2. The member has neuroendocrine pancreatic tumor which is resectable.
3. Member has disease progression while taking Afinitor (everolimus).
4. Dosing exceeds single dose limit of Afinitor (everolimus) 10 mg.
5. Do not exceed 120 (2.5 mg) tablets/month, 60 (5 mg) tablets/month, 30 (7.5 mg) tablets/month, or 30 (10 mg) tablets/month.
6. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature may be deemed as not approvable and therefore not reimbursable.

IV. PROCEDURE

Requests for Afinitor (everolimus) shall be reviewed for appropriateness per FDA approved product labeling, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) clinical guidelines, or CMS approved compendia.

1. **Dosage and Administration**
    a. Breast cancer, Advanced, hormone receptor-positive, HER2 negative, in combination with exemestane after failure with letrozole or anastrozole: 10 mg orally once daily.
    b. Neuroendocrine tumor, Pancreatic, unresectable, locally advanced, or metastatic disease: 10 mg orally once daily.
    c. Renal cell carcinoma, advanced disease after failure of treatment with sunitinib or sorafenib: 10 mg orally once daily.
    d. Subependymal giant cell astrocytoma - Tuberous sclerosis syndrome: .5 mg/m2 PO once daily initially, then titrate dose to achieve a target trough level of 5—15 ng/ml. Once stable dose and trough level is attained, trough concentrations can be measured every 3 to 6 months (changing body surface area) or every 6 to 12 months (stable body surface area)
2. **Dosage Adjustments**

Patients with advanced breast cancer, advanced, renal cell cancer or advanced neuroendocrine tumors (NET) or renal angiomyolipoma with tuberous sclerosis complex:

a. **Patients with Hepatic Impairment Dosing**
For patients being treated for renal cell cancer or advanced pancreatic neuroendocrine tumors who have mild hepatic impairment (Child-Pugh class A), reduce 7.5 mg PO daily if not tolerated reduce to 5 mg PO daily. For moderate hepatic impairment (Child-Pugh class B), reduce Afinitor dose to 5 mg PO once daily if not tolerated reduce to 2.5 mg PO daily. For severe impairment (Child-Pugh class C), do not exceed dose of 2.5 mg daily.

b. **Patients with Renal Impairment Dosing**
Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

c. **Adults receiving strong inducers of CYP3A4/P-glycoprotein inducer:** Avoid co administration if possible. If a strong CYP3A4 is required, 10 mg PO once daily initially then

consider increasing the dose by 5 mg increments up to 20 mg PO once daily. If the strong inducer is discontinued, resume the everolimus dose used prior to the initiation of the strong inducer after 3-5 days washout period. NOTE: Dosage adjustment is based on pharmacokinetic data; no clinical data are available with this dosage adjustment.

d. **Adults receiving moderate CYP3A4 and/or P-glycoprotein inhibitors:** Reduce the dose to 2.5 mg PO daily. A dose increase to 5 mg PO daily may be considered based on patient tolerance. If the moderate inhibitor is discontinued, allow a 2—3 day washout period before increasing the Afinitor dose; restart the Afinitor dose used before the initiation of the moderate CYP3A4 and/or P-glycoprotein inhibitor.

e. **Patients with nonhematologic toxicities:** Reduce dose to alternate-day dosing if dose reduction is below the lowest available strength. For grade 2, interrupt therapy until symptoms are improved to grade 1 or less then reinitiate at approximately 50% of the previous dose. If the patient fails to recover within 4 weeks, discontinue treatment. For grade 3, interrupt therapy until symptoms improve to grade 1 or less then reinitiate at 50% of the previous dose. If toxicity recurs at grade 3 or 4, discontinue therapy.

f. **Stomatitis**: Reduce dose to alternate-day dosing if dose reduction is below the lowest available strength. For grade 2, interrupt therapy until symptoms are improved to grade 1 or less then reinitiate at same dose. If grade 2 symptoms recur, interrupt therapy until symptoms improve to grade 1 or less and reinitiate at approximately 50% of the previous dose. For grade 3 symptoms, interrupt therapy until symptoms are improved to grade 1 or less then reinitiate at approximately 50% of the previous dose. For grade 4, discontinue therapy.

g. **Severe or intolerable adverse events**: Reduce dose temporarily by about 50% and/or interrupt therapy. Implement alternate-day dosing, if dose reduction is below the lowest available strength is required.

Patients with subependymal giant cell astrocytoma (SEGA)

a. **Adults, Adolescents, and Children >= 3 years receiving strong inducers of CYP3A4/P-glycoprotein:** Avoid co administration if possible. If a concomitant strong CYP3A4 inducer is required, double the Afinitor dose. Individualize subsequent dosing based on therapeutic drug monitoring. If the strong CYP3A4 inducer is discontinued, adjust the everolimus dose to the one used before initiation of the CYP3A4 inducer and assess the everolimus trough concentration approximately 2 weeks later.

b. **Adults, Adolescents, and Children >= 3 years receiving moderate CYP3A4 and/or P-glycoprotein inhibitor:** If a concomitant moderate CYP3A4 or P-glycoprotein inhibitor is required, reduce the dose by approximately 50% to maintain trough concentrations of 5—10 ng/ml. If dose reduction is needed for patients taking 2.5 mg PO daily, consider alternate day dosing. Assess everolimus trough concentrations approximately 2 weeks after the addition of a moderate CYP3A4 and/or P-glycoprotein inhibitor. Individualize subsequent dosing based on therapeutic drug monitoring. If the moderate inhibitor is discontinued, adjust the everolimus dose to the one used before initiation of the moderate CYP3A4 and/or P-glycoprotein inhibitor and assess the everolimus trough concentration approximately 2 weeks later.

c. **Patients with Hepatic Impairment Dosing:** For patients with mild to moderate hepatic impairment (Child-Pugh class A or B), initial dose adjustment may not be required. For severe impairment (Child-Pugh class C), reduce initial dose to 2.5 mg/m^2 PO daily. Maintain trough concentrations of 5—10 ng/ml for all levels of impairment. Implement alternate-day dosing, if dose reduction is below the lowest available strength is required.

d. **Severe or intolerable adverse events**: Reduce dose temporarily by about 50% and/or interrupt therapy. Implement alternate-day dosing, if dose reduction is below the lowest available strength is required.

3. **Monitoring**

a. Lipid panel; prior to therapy initiation and periodically during treatment.

b. Renal function (BUN measurement, serum creatinine, urinary protein); prior to therapy initiation and periodically during treatment.

c. Localized and systemic infections caused by opportunistic pathogens.

d. Noninfectious pneumonitis (hypoxia, pleural effusion, cough, or dyspnea without clinical causation or radiologic changes).

V. APPROVAL AUTHORITY

1. Review – Utilization Management Department
2. Final Approval – Utilization Management Committee

VI. ATTACHMENTS

None

VII. REFERENCES

1. Afinitor prescribing information. Novartis Pharmaceutical Corporation. East Hanover, NJ. 2018.
2. Clinical Pharmacology Elsevier Gold Standard. 2020.
3. Micromedex® Healthcare Series: Thomson Micromedex, Greenwood Village, Co. 2020.
4. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium. 2020.
5. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD. 2020.