



CIGNA PHARMACY COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Effective Date.....10/15/2010
Next Review Date.....10/15/2011
Coverage Policy Number9015

Subject **Everolimus (Afinitor®)**

Table of Contents

Coverage Policy 1
General Background 2
Coding/Billing Information 3
References 3

Hyperlink to Related Coverage Policies

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

CIGNA covers everolimus (Afinitor®) as medically necessary for the treatment of advanced renal cell carcinoma (RCC) when there is a failure, contraindication, or intolerance to sunitinib (Sutent®) or sorafenib (Nexavar®).

FDA Approved Indications

Afinitor is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib.

FDA Recommended Dosing

The recommended dose of Afinitor for treatment of advanced RCC is 10 mg, to be taken once daily at the same time every day, either with or without food. Continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs. Management of severe and/or intolerable adverse reactions may require temporary dose reduction and/or interruption of Afinitor therapy. If dose reduction is required, the suggested dose is 5 mg daily.

Drug Availability

Afinitor is available in a 5 mg tablet (white to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with "5" on one side and "NVR" on the other) or a 10 mg tablet (white to slightly

yellow, elongated tablets with a bevelled edge and no score, engraved with “UHE” on one side and “NVR” on the other).

General Background

Pharmacology

Everolimus is an orally administered kinase inhibitor labeled for the treatment of advanced RCC after treatment with sunitinib or sorafenib has failed. Everolimus, a rapamycin derivative, inhibits mTOR (mammalian target of rapamycin), an important regulator of cell growth and proliferation. Inhibition of mTOR results in reduced angiogenesis, cell proliferation, and glucose uptake. Peak plasma concentrations are achieved 1 to 2 hours after oral administration. Everolimus is approximately 74% protein-bound. Everolimus is metabolized by CYP3A4 and is a substrate of P-glycoprotein. Everolimus has a half-life of 30 hours and is eliminated primarily in feces as metabolites.

Guidelines

The National Comprehensive Cancer Network (NCCN) recommends afinitor for RCC for subsequent therapy as a single agent for relapsed or medically unresectable stage IV disease with predominant clear cell histology in patients who have progressed on prior tyrosine kinase inhibitor (eg, sunitinib or sorafenib) therapy (grade 1).

Clinical Efficacy

There are no published trials comparing everolimus to other agents in RCC. One published randomized, multi-center trial (n=410) demonstrated efficacy of everolimus 10 mg daily compared to placebo in patients with metastatic RCC whose disease had progressed on sunitinib, sorafenib, or both. After an interim analysis, the trial was halted early due to favorable response. Progression-free survival, was significantly improved in the everolimus group compared with placebo ($p<0.0001$). The median progression-free survival was 4 months in everolimus-treated patients and 1.9 months in placebo-treated patients. Updated results, which include additional data gathered after the interim analysis cutoff up to the time of unblinding, are available and are consistent with the earlier analysis. The median progression-free survival in the updated analysis was 4.9 months with everolimus compared to 1.9 months with placebo ($p<0.0001$). There are no published trials comparing everolimus to other agents in RCC.

One published, open-label, case series evaluated everolimus in metastatic RCC. Forty-one patients with metastatic RCC (predominantly clear-cell) who had received ≤ 1 prior treatment regimen for their disease (chemotherapy, immunotherapy, or non-mTOR molecular targeted therapy) were enrolled. Patients received everolimus 10 mg daily for 8 weeks or until disease progression. The median progression-free survival was 11.2 months. Approximately 70% of patients reported a progression-free survival of at least 6 months. There were no complete responses. Clinical response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST). Of the 37 patients evaluated for response, 5/37 achieved a partial response, 27/37 achieved stable disease of at least 3 months duration, and 21/27 stable disease of at least 6 months duration. Five patients reported progressive disease or stable disease of ≤ 3 months. Median overall survival was 22.1 months.

Subset analyses revealed the treatment effect was maintained regardless of age, sex, geographic region, or previous treatment (sorafenib, sunitinib, or both).

Adverse Reactions

Serious adverse events include non-infectious pneumonitis and serious infections. The most common adverse events include stomatitis, infections, asthenia, fatigue, cough, diarrhea, and rash. The most frequently reported laboratory abnormalities include decreased hemoglobin, increased cholesterol, and increased triglycerides. Everolimus is a substrate and inhibitor of CYP3A4 and P-glycoprotein and a mixed inhibitor of CYP2D6. Avoid concomitant use of everolimus with moderate to strong CYP3A4 and P-glycoprotein inhibitors.

Coding/Billing Information

Note: This section is not in use.

References

1. Amato RJ, Jac J, Giessinger S, Saxena S, Willis JP. A phase 2 study with a daily regimen of the oral mTOR inhibitor RAD001 (everolimus) in patients with metastatic clear cell renal cell cancer. *Cancer*. Mar 20 2009.
2. Awada A, Cardoso F, Fontaine C, et al. The oral mTOR inhibitor RAD001 (everolimus) in combination with letrozole in patients with advanced breast cancer: results of a phase I study with pharmacokinetics. *Eur J Cancer*. Jan 2008;44(1):84-91.
3. Baselga J, Semiglazov V, van Dam P, et al. Phase II randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with estrogen receptor-positive breast cancer. *J Clin Oncol*. Jun 1 2009;27(16):2630-2637.
4. Campone M, Levy V, Bourbouloux E, et al. Safety and pharmacokinetics of paclitaxel and the oral mTOR inhibitor everolimus in advanced solid tumours. *Br J Cancer*. Jan 27 2009;100(2):315-321.
5. Chapman TM, Perry CM. Everolimus. *Drugs*. 2004;64(8):861-872.
6. Cohen HT, McGovern FJ. Renal-cell carcinoma. *N Engl J Med*. Dec 8 2005;353(23):2477-2490.
7. Fouladi M, Laningham F, Wu J, et al. Phase I study of everolimus in pediatric patients with refractory solid tumors. *J Clin Oncol*. Oct 20 2007;25(30):4806-4812.
8. Gupta K, Miller JD, Li JZ, Russell MW, Charbonneau C. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. *Cancer Treat Rev*. May 2008;34(3):193-205.
9. Kay A, Motzer R, Figlin R, et al. Updated data from a phase III randomized trial of everolimus (RAD001) versus PBO in metastatic renal cell carcinoma (mRCC). Abstract 278. Paper presented at: 2009 Genitourinary Cancers Symposium February 26-29, 2009;Orlando, Florida. http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=64&abstractID=20488. Accessed June 2, 2009.
10. Kroog GS, Motzer RJ. Systemic therapy for metastatic renal cell carcinoma. *Urol Clin North Am*. Nov 2008;35(4):687-701; ix.
11. McEvoy GK, ed. AHFS 2010 Drug Information. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc; 2010.
12. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet*. Aug 9 2008;372(9637):449-456.
13. NCCN Drugs & Biologics Compendium™. Afinitor® (everolimus). Copyright 2010, National Comprehensive Cancer Network (NCCN).

14. Novartis Pharmaceuticals Corporation. Everolimus (Afinitor®) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation. July 2010.
15. O'Donnell A, Faivre S, Burris HA, 3rd, et al. Phase I pharmacokinetic and pharmacodynamic study of the oral mammalian target of rapamycin inhibitor everolimus in patients with advanced solid tumors. *J Clin Oncol*. Apr 1 2008;26(10):1588-1595.
16. Rini BI, Campbell SC, Escudier B. Renal cell carcinoma. *Lancet*. Mar 28 2009;373(9669):1119-1132.
17. Rini BI, Halabi S, Rosenberg JE, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *J Clin Oncol*. Nov 20 2008;26(33):5422-5428.
18. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res*. Oct 1 2004;64(19):7099-7109.
19. Wolpin BM, Hezel AF, Abrams T, et al. Oral mTOR inhibitor everolimus in patients with gemcitabine-refractory metastatic pancreatic cancer. *J Clin Oncol*. Jan 10 2009;27(2):193-198.
20. Yao JC, Phan AT, Chang DZ, et al. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. *J Clin Oncol*. Sep 10 2008;26(26):4311-4318.
21. Yee KW, Zeng Z, Konopleva M, et al. Phase I/II study of the mammalian target of rapamycin inhibitor everolimus (RAD001) in patients with relapsed or refractory hematologic malignancies. *Clin Cancer Res*. Sep 1 2006;12(17):5165-5173.

"CIGNA" and the "Tree of Life" logo are registered service marks of CIGNA Intellectual Property, Inc., licensed for use by CIGNA Corporation and its operating subsidiaries. All products and services are provided exclusively by such operating subsidiaries and not by CIGNA Corporation. Such operating subsidiaries include Connecticut General Life Insurance Company, CIGNA Behavioral Health, Inc., Intracorp, and HMO or service company subsidiaries of CIGNA Health Corporation and CIGNA Dental Health, Inc. In Arizona, HMO plans are offered by CIGNA HealthCare of Arizona, Inc. In California, HMO plans are offered by CIGNA HealthCare of California, Inc. and Great-West Healthcare of California, Inc. In Connecticut, HMO plans are offered by CIGNA HealthCare of Connecticut, Inc. In North Carolina, HMO plans are offered by CIGNA HealthCare of North Carolina, Inc. In Virginia, HMO plans are offered by CIGNA HealthCare Mid-Atlantic, Inc. All other medical plans in these states are insured or administered by Connecticut General Life Insurance Company.

Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.