Introduction

Genes contain instructions for how a cell makes proteins. Proteins control the functions within a cell. The mTOR kinase protein helps guide how cells grow. mTOR kinase protein can also send signals for the body to create new blood vessels. When something goes wrong with the mTOR kinase protein, cells can grow and divide without stopping, forming a tumor. Problems with the mTOR kinase protein also can stimulate new blood vessels that a tumor needs. Drugs called mTOR kinase inhibitors interrupt the signals telling cancer cells and blood vessels to grow. This policy discusses when mTOR kinase inhibitors may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Note: Initial approval period for oral drugs listed below will be 3 months. Continued approval beyond the first 3 months will require documentation showing objective response to therapy.

Note: Initial approval period for injectable drugs listed below will be 12 months.
## Use of mTOR Kinase Inhibitors in Cancer Patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Drugs</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Afinitor® (rverolimus)</strong></td>
<td><strong>Afinitor® (rverolimus) may be considered medically necessary for the labeled indications:</strong></td>
</tr>
<tr>
<td></td>
<td>• Treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole</td>
</tr>
<tr>
<td></td>
<td>• Advanced renal cell carcinoma (RCC) after treatment failure with Sutent® (sunitinib) or Nexavar® (sorafenib)</td>
</tr>
<tr>
<td></td>
<td>• Progressive neuroendocrine tumors of pancreatic origin with unresectable locally advanced or metastatic disease</td>
</tr>
<tr>
<td></td>
<td>• Subependymal giant cell astrocytoma (SEGA) in patients with tuberous sclerosis</td>
</tr>
<tr>
<td></td>
<td>• Renal angiomyolipoma with tuberous sclerosis complex (TSC) not requiring immediate surgery</td>
</tr>
<tr>
<td></td>
<td>• Neuroendocrine tumor (NET) of the stomach and intestine (gastrointestinal) or lung that has progressed and cannot be treated with surgery.</td>
</tr>
</tbody>
</table>

**Note:** Everolimus is not for use in people with carcinoid tumors that actively produce hormones.

**Afinitor® (rverolimus) may be considered medically necessary for off-label use in treating:**

- Waldenström’s macroglobulinemia/lymphoplasmacytic lymphoma (NCCN Category 2A)
- Advanced neuroendocrine tumors. (NCCN Category 2A)
- Advanced renal cell carcinoma (RCC) for patients who have progressed on prior tyrosine kinase inhibitor therapy (not limited to Sutent® (sunitinib) or Nexavar® (sorafenib), or as first-line therapy in patients with relapse or unresectable metastatic disease with non-clear cell histology.
- Hodgkin lymphoma, as single agent second-line or salvage therapy
## Drug Medical Necessity

- Lung neuroendocrine tumors
- Soft tissue sarcoma - PEComa/Recurrent angiomyolipoma/Lymphangioleiomyomatosis, as single-agent therapy. (NCCN Category 2A)

All other uses of Afinitor® (rverolimus) are considered investigational.

### Injectable Drugs

**Torisel® (temsirolimus)**

Torisel® (temsirolimus) may be considered medically necessary for the labeled indication, treatment of patients with advanced renal cell carcinoma (RCC).

Torisel® (temsirolimus) may be considered medically necessary for off-label use in treating endometrial carcinoma.

All other uses of Torisel® (temsirolimus) are considered investigational.

### Use of mTOR Kinase Inhibitors in Organ Transplant Patients

#### Oral Drugs

**Zortress® (everolimus)**

Zortress® (everolimus)* is considered medically necessary for prophylaxis of organ rejection in allogeneic transplant patients.

*Note: This form of Zortress® (everolimus) does NOT require a prior authorization.

**Prograf® (tacrolimus)**

Prograf® (tacrolimus)* is considered medically necessary for the prophylaxis of organ rejection in patients receiving allogeneic transplants.

*Note: This drug does NOT require a prior authorization.

**Rapamune® (sirolimus)**

Rapamune® (sirolimus)* is considered medically necessary for the prophylaxis of organ rejection in patients receiving allogeneic transplants.

*Note: This drug does NOT require a prior authorization.
Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J7507</td>
<td>Tacrolimus (Prograf®), oral, per 1 mg.</td>
</tr>
<tr>
<td>J7520</td>
<td>Sirolimus (Rapamune®), oral, 1 mg</td>
</tr>
<tr>
<td>J7527</td>
<td>Everolimus (Zortress®), oral, 0.25 mg</td>
</tr>
<tr>
<td>J9330</td>
<td>Injection, Temsirolimus (Torisel®), 1 mg</td>
</tr>
</tbody>
</table>

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Related Information

Benefit Application

The drugs included in this policy may be covered under either the pharmacy or medical benefit.

Evidence Review

Description

The mammalian target of rapamycin (mTOR), also known as mechanistic target of rapamycin or FKS06 binding protein 12-rapamycin associated protein 1 (FRAP1), is a protein which is encoded by the FRAP1 gene. mTOR is a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription. mTOR belongs to the phosphatidylinositol 3-kinase-related kinase protein family. It is downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers including clear cell renal cell carcinoma (RCC).
Afinitor® (everolimus) and Torisel® (temsirolimus) bind to an intracellular protein, FKBP-12, forming a complex that inhibits mTOR kinase activity, modulates hypoxia-inducible factor (HIF-1), and reduces the expression of VEGF. Inhibition of mTOR by Afinitor® (everolimus) has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in in vitro and/or in vivo studies.

This blockade inhibits T cell activation and proliferation, IL-6 stimulated B cell activation, proliferation, and antibody production, as well as proliferation of non-immune cells like smooth muscle cells. mTOR inhibitors, Prograf® (tacrolimus), Rapamune® (sirolimus) and most recently Zortress® (everolimus), have proved useful immunosuppressants to prevent transplant rejection.

Afinitor® (everolimus) is indicated for the treatment of patients with advanced RCC after treatment failure with Sutent® (sunitinib) or Nexavar® (sorafenib).

Torisel® (temsirolimus) is indicated for the treatment of advanced renal cell carcinoma.

Afinitor® (everolimus) is indicated for prophylaxis of organ rejection in adult patients at low–moderate immunologic risk receiving a kidney transplant, and for use in combination with basiliximab and concurrently with reduced doses of cyclosporine and corticosteroids. Use in patients at high immunologic risk is not established. Use for prophylaxis in organs other than kidney is not established. Safety and efficacy in pediatric patients (<18 years) has not been established.

Tacrolimus® (prograf) is indicated for the prophylaxis of organ rejection in patients receiving allogeneic liver, kidney, or heart transplants. It is recommended that prograf be used concomitantly with adrenal corticosteroids. Because of the risk of anaphylaxis, prograf injection should be reserved for patients unable to take prograf capsules orally. In heart and kidney transplant recipients, it is recommended that prograf be used in conjunction with azathioprine or mycophenolate mofetil. The safety and efficacy of the use of prograf with sirolimus have not been established.

Rapamune® (sirolimus) is indicated for the prophylaxis of organ rejection in patients aged ≥13 years receiving renal transplants. In patients at low-to moderate-immunologic risk, it should be used initially with cyclosporine (CsA) and corticosteroids. CsA withdrawal is recommended 2–4 months after transplantation. In patients at high-immunologic risk, it should be used in combination with cyclosporine and corticosteroids for the first 12 months following transplantation. Safety and efficacy of CsA withdrawal has not been established in high risk patients. Therapeutic drug monitoring is recommended for all patients.
Renal Cell Carcinoma

Renal cell cancer (RCC) is a heterogeneous disease consisting of several types of cancer occurring in the kidney. The most common forms of RCC are clear cell (75%) and papillary types 1 and 2 (12-15%). Other more rare forms of RCC include chromophobe, oncocytoma, and Bellini (collecting) duct types. In 2009, it was estimated approximately 58,000 new cases of RCC would be diagnosed and approximately 13,000 Americans would die of RCC. The age-adjusted incidence of RCC is 13.6 per 100,000 Americans, with men being more commonly affected than women at a ratio of 1.5-2.0 to 1. From 2002 to 2006, median age at diagnosis was 64 years.

Pharmacotherapy

Management of RCC varies largely by staging and risk group stratification. Surgery (either radical nephrectomy or nephron-sparing procedures) is the standard of care for treatment of early stage (localized) RCC (Stages I-III). Neither radiation nor adjuvant therapies have been found beneficial for localized RCC after resection. About 20-30% of patients with localized RCC relapse after surgery.

In advanced disease (Stage IV), surgery with systemic pharmacotherapy is recommended. Chemotherapy and hormonal agents have been found to have minimal efficacy against metastatic RCC. Chemotherapy response rates range from 4-12%, and typically responses were only of brief duration. Hormonal agents have been shown to provide about a 2% response rate. Consequently, use of these therapies was replaced by the cytokines interferon alfa and aldesleukin (IL-2). High dose IL-2 is the only drug to date that has resulted in durable remissions in RCC. Unfortunately, response rates for the cytokines are still low, ranging from 20-25%. In addition, their use may be limited by toxicities.

Recent advance in the understanding of the pathophysiology of RCC has led to development of targeted therapies and improved outcomes (PFS and overall survival) in metastatic RCC. Targeted new therapies include the tyrosine kinase inhibitors Nexavar® (sorafenib) and Sutent® (sunitinib), the VEGF inhibitor Avastin® (bevacizumab), and the mTOR inhibitors Afinitor® (everolimus) and Torisel® (temsirolimus).

The von Hippel-Lindau (VHL) gene is a tumor suppressor gene that has been implicated in the development of clear cell renal carcinoma, the most common form of RCC. This gene’s protein byproduct is a critical component of a cellular pathway that regulates changes in oxygen availability through control of hypoxia-inducible factor (HIF). HIF is responsible for downstream production of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF),
and transforming growth factor (TGF) which each play a role in angiogenesis and the growth of renal cell tumors. In addition to VHL, up-regulation of HIF is also modulated by growth factor and cell adhesion pathways (phosphatidylinositol 3-kinase [P13K]/Akt/mTOR and Ras/Raf/mitogen-activated kinase).

Everolimus is only indicated for second-line treatment of advanced (Stage IV) RCC after failure with a VEGF-TKI (sorafenib or sunitinib). Currently, adjuvant therapy is not recommended outside of a clinical trial setting for patients with localized disease (Stages I-III) who have undergone complete resection; observation remains the standard of care in this subpopulation.

Efficacy

Afinitor® (everolimus)

At the time of review, there were no available head-to-head clinical trials between everolimus and other pharmacotherapeutic alternatives for first- or second-line therapy of advanced RCC.

The efficacy of Afinitor® (everolimus) for the treatment of metastatic RCC progressing after or during treatment with a VEGF-TKI was established in one Phase III level 1 trial (RECORD-1). Four hundred four patients were randomized 2:1 to treatment with everolimus 10 mg daily or placebo orally in combination with best supportive care. The study was terminated early because an interim analysis showed significantly greater progression-free survival (PFS) in favor of active treatment (median PFS was 4.0 months [95% CI 3.7–5.5] for the everolimus-treated group vs. 1.9 months [1.8–1.9] for the placebo-treated group).

The efficacy results from RECORD-1 for everolimus have not been indirectly compared with those from the phase III trial for temsirolimus because the patient populations and methodologies in these trials were significantly different. At baseline, patients in the temsirolimus trial were predominately high-risk and previously untreated while those in the everolimus trial were primarily intermediate-risk and were previously treated with a VEGF-TKI. In addition, RECORD-1 was placebo-controlled while the temsirolimus trial was actively controlled with interferon alfa and a combination of interferon alfa and temsirolimus.

Two additional Phase II single-arm clinical trials were found in the medical literature supporting the efficacy of everolimus as monotherapy for prolonging PFS in patients with progressive metastatic clear cell RCC following a VEGF-TKI and efficacy in combination with bevacizumab for patients with metastatic or unresectable locally recurrent clear cell RCC. Phase I trials were excluded from this efficacy analysis.
The relative efficacy of everolimus with other pharmacotherapeutic alternatives for the treatment of patients with RCC cannot be established with certainty at this time.

Torisel® (temsirolimus)

A Phase III, multi-center, three-arm, randomized, open-label study was conducted in previously untreated patients with advanced renal cell carcinoma (clear cell and non-clear cell histologies). The objectives were to compare Overall Survival (OS), Progression-Free Survival (PFS), Objective Response Rate (ORR), and safety in patients receiving IFN-α to those receiving Torisel or Torisel plus IFN-α. Patients in this study had 3 or more of 6 pre-selected prognostic risk factors (less than one year from time of initial RCC diagnosis to randomization, Karnofsky performance status of 60 or 70, hemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, lactate dehydrogenase > 1.5 times the upper limit of normal, and more than one metastatic organ site).

Patients were stratified for prior nephrectomy status within three geographic regions and were randomly assigned (1:1:1) to receive IFN-α alone (n=207), Torisel alone (25 mg weekly; n=209), or the combination arm (n=210). The ITT population for this interim analysis included 626 patients. Demographics were comparable between the three treatment arms with regard to age, gender, and race. The mean age of all groups was 59 years (range 23-86). Sixty-nine percent were male and 31% were female. The racial distribution for all groups was 91% White, 4% Black, 2% Asian, and 3% other. Sixty-seven percent of patients had a history of prior nephrectomy. The median duration of treatment in the TORISEL arm was 17 weeks (range 1-126 weeks). The median duration of treatment on the IFN arm was 8 weeks (range 1-124 weeks).

There was a statistically significant improvement in OS (time from randomization to death) in the TORISEL 25 mg arm compared to IFN-α. The combination of Torisel 15 mg and IFN-α did not result in a significant increase in overall survival when compared with IFN-α alone. The evaluations of PFS (time from randomization to disease progression or death) and ORR were based on blinded independent radiologic assessment of tumor response.

Safety

As with relative efficacy, the relative safety and tolerability of everolimus with other pharmacotherapeutic alternatives for the treatment of patients with RCC cannot be conclusively established at this time due to the lack of head-to-head comparisons and the variability in baseline patient populations and study methodologies in key clinical trials for these agents.
Based on results from the pivotal RECORD-1 trial, Afinitor® (everolimus) in combination with best supportive care was associated with more toxicity than placebo plus best supportive care. The rates of permanent discontinuation due to toxicity were 14% for the Afinitor and 3% for the placebo treatment groups. The most common adverse reactions (irrespective of causality) leading to treatment discontinuation were pneumonitis and dyspnea. Deaths due to acute respiratory failure (0.7%), infection (0.7%) and acute renal failure (0.4%) were observed in everolimus-treated patients but none were observed in the placebo-treated group.

As with all rapamycin derivatives, everolimus is associated with development of serious non-infectious pneumonitis and infections, as well as inhibition of mTOR regulated glucose and lipid metabolism that may result in hyperglycemia and hyperlipidemia.

The most commonly reported (observed at an incidence ≥30%) adverse events following exposure to everolimus in clinical trials irrespective of relationship to treatment include stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common laboratory abnormalities (incidence ≥50%) include anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine.

The most common grade 3/4 toxicities (incidence ≥3%) are infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common grade 3/4 laboratory abnormalities (incidence ≥3%) are lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia.

2012 Update

No information was found that would prompt a change in policy statements.

2013 Update

Policy was updated to include new FDA-labeled and NCCN recommendations for everolimus for metastatic breast cancer, pancreatic neuroendocrine tumors, recurrent angiomyolipoma / Lymphangioleiomyomatosis, and renal cell carcinoma after treatment with any TKI, not necessarily sorafenib or sunitinib.
2014 Update

Policy was updated to include new NCCN recommendations for neuroendocrine tumors and endometrial carcinoma.

2015 Update

No information was found that would prompt a change in policy statements.

References


**History**

<table>
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<tr>
<th>Date</th>
<th>Comments</th>
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</thead>
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<td>05/10/11</td>
<td>Add to Prescription Drug Section - New Policy.</td>
</tr>
<tr>
<td>01/27/12</td>
<td>HCPCS code J8561 added to policy.</td>
</tr>
<tr>
<td>07/20/12</td>
<td>Replace policy. Policy updated with literature review; no change in policy statements. HCPCS codes J7507, J7520 and J9330 added to coding section.</td>
</tr>
<tr>
<td>10/14/13</td>
<td>Replace policy. Policy updated to include new FDA-labeled and NCCN recommendations for everolimus for metastatic breast cancer, pancreatic neuroendocrine tumors, recurrent angiomyolipoma / lymphangioleiomyomatosis, and renal cell carcinoma after treatment with any TKI, not necessarily sorafenib or sunitinib.</td>
</tr>
<tr>
<td>11/10/14</td>
<td>Annual review. Policy updated to include new NCCN recommendations for neuroendocrine tumors and endometrial carcinoma.</td>
</tr>
<tr>
<td>09/08/15</td>
<td>Annual review. Policy updated with literature review; reference 19 added. Medically necessary policy statement for everolimus (Afinitor®) updated to include labelled indication for renal angiomyolipoma with tuberous sclerosis complex (TSC).</td>
</tr>
<tr>
<td>10/01/16</td>
<td>Annual review, approved September 13, 2016: Inclusion of a new indication for Afinitor.</td>
</tr>
<tr>
<td>06/01/17</td>
<td>Annual Review, approved May 23, 2017. A statement outlining the length of therapy for initial approval has been added to the policy.</td>
</tr>
<tr>
<td>11/14/17</td>
<td>Coding updated, removed HCPCS code J8561 and added HCPCS code J7527. Minor formatting updates were made.</td>
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**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review
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