

## PHARMACY / MEDICAL POLICY – 5.01.533

## mTOR Kinase Inhibitors

Effective Date: June 1, 2018

Last Revised: May 3, 2018


Replaces: N/A

RELATED MEDICAL POLICIES:

None

Select a hyperlink below to be directed to that section.

[POLICY CRITERIA](#) | [CODING](#) | [RELATED INFORMATION](#)  
[EVIDENCE REVIEW](#) | [REFERENCES](#) | [HISTORY](#)

 Clicking this icon returns you to the hyperlinks menu above.

---

## 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

Drug	Medical Necessity
<b>Oral Drugs</b>	
<p><b>Afinitor® tablet for oral administration, (everolimus), Afinitor® Disperz (everolimus) tablet for oral suspension</b></p>	<p><b>Afinitor® (everolimus) may be considered medically necessary for treatment of the labeled indications:</b></p> <ul style="list-style-type: none"> <li>• Postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer, in combination with exemestane after failure of treatment with letrozole or anastrozole</li> <li>• Adults with advanced renal cell carcinoma (RCC) after treatment failure with Sutent® (sunitinib) or Nexavar® (sorafenib)</li> <li>• Adults with progressive, unresectable neuroendocrine tumors (NET) of pancreatic (PNET), gastrointestinal or lung origin</li> <li>• Adults with renal angiomyolipoma with tuberous sclerosis complex (TSC) not requiring immediate surgery</li> </ul> <p><b>Afinitor® and Afinitor® Disperz may be considered medically necessary for the labeled indication:</b></p> <ul style="list-style-type: none"> <li>• Treatment of pediatric and adult patients with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected</li> </ul> <p><b>Afinitor® Disperz may be considered medically necessary for the labeled indication:</b></p> <ul style="list-style-type: none"> <li>• Adult and pediatric patients aged 2 years and older with TSC-associated partial-onset seizures</li> </ul> <p><b>Note:</b> Everolimus is not labeled for use in people with carcinoid tumors that actively produce hormones. NCCN assigns these a Category 2A recommendation.</p> <p><b>All other uses of Afinitor® (everolimus) are considered investigational.</b></p>
<b>Injectable Drugs</b>	



Drug	Medical Necessity
<b>Torisel® (temsirolimus)</b>	<p><b>Torisel® (temsirolimus) may be considered medically necessary for the labeled indication, treatment of patients with advanced renal cell carcinoma (RCC) #.</b></p> <p><b>All other uses of Torisel® (temsirolimus) are considered investigational.</b></p>

## Use of mTOR Kinase Inhibitors in Organ Transplant Patients

Drug	Medical Necessity
<b>Oral Drugs</b>	
<b>Zortress® (everolimus)</b>	<p><b>Zortress® (everolimus)* is considered medically necessary for prophylaxis of organ rejection in allogeneic transplant patients:</b></p> <p><b>*Note:</b> This form of Zortress® (everolimus) does NOT require a prior authorization.</p>
<b>Prograf® (tacrolimus)</b>	<p><b>Prograf® (tacrolimus)*# is considered medically necessary for the prophylaxis of organ rejection in patients receiving allogeneic transplants<sup>a</sup>.</b></p> <p><b>*Note:</b> This drug does NOT require a prior authorization.</p>
<b>Rapamune® (sirolimus)</b>	<p><b>Rapamune® (sirolimus)* is considered medically necessary for:</b></p> <ul style="list-style-type: none"> <li>• Prophylaxis of organ rejection in patients receiving allogeneic transplants.</li> <li>• Treatment of patients with lymphangiomyomatosis</li> </ul> <p><b>*Note:</b> This drug does NOT require a prior authorization.</p>

## Coding

Code	Description
------	-------------



Code	Description
<b>CPT</b>	
J9330	Injection, Temsirolimus (Torisel®), 1 mg

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

## 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 FK506 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 Zortress® (everolimus), have proved useful immunosuppressants to prevent transplant rejection.

Afinitor® (everolimus) is indicated for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole, adults with progressive neuroendocrine tumors of pancreatic origin (PNET) and adults with progressive, well-differentiated, non-functional neuroendocrine tumors (NET) of gastrointestinal or lung origin that are unresectable, adults with advanced RCC after treatment failure with Sutent® (sunitinib) or Nexavar® (sorafenib), and adults with renal angiomyolipoma and tuberous sclerosis complex (TSC) not requiring immediate surgery

Afinitor® (everolimus) and Afinitor® Disperz (everolimus tablet for oral suspension) are indicated for the treatment of pediatric and adult patients with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.

Torisel® (temsirolimus) is indicated for the treatment of advanced renal cell carcinoma. Patients should be premedicated with IV diphenhydramine (or another similar antihistamine) about 30 minutes before each dose of Torisel®.

Zortress® (everolimus) is indicated for prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney or liver transplant. Safety and efficacy in kidney transplant patients at high immunologic risk, pediatric patients (<18 years), or recipients of transplanted organs other than kidney or liver have not been established. Kidney transplant patients should start Zortress immediately after transplantation. Zortress should be used in combination with basiliximab, cyclosporine (reduced doses), and corticosteroids in kidney transplant patients. Liver transplant patients should start Zortress no earlier than 30 days after transplantation. Zortress should be used in combination with tacrolimus (reduced doses) and corticosteroids in liver transplant patients.

Prograf® (tacrolimus) 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. Prograf should not be used simultaneously with cyclosporine. The safety and efficacy of the use of prograf with sirolimus in kidney transplant have not been established. Use of Prograf with sirolimus is not recommended in liver and heart transplant. Careful and frequent monitoring of tacrolimus trough concentration is recommended. Black



patients may require higher doses in order to achieve comparable trough concentration. Rapamune® (sirolimus) is indicated for the prophylaxis of organ rejection in patients aged  $\geq 13$  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)**

#### ***Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer***

A randomized, double-blind, multicenter study (BOLERO-2, NCT00863655) of AFINITOR plus exemestane versus placebo plus exemestane was conducted in 724 postmenopausal women with estrogen receptor-positive, HER2/neu-negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. The primary endpoint for the trial was progression-free survival (PFS) evaluated by Response Evaluation Criteria In Solid Tumors (RECIST), based on investigator (local radiology) assessment. The median progression-free survival by investigator assessment at the time of the final PFS analysis was 7.8 and 3.2 months in the AFINITOR and placebo arms, respectively [HR = 0.45 (95% CI: 0.38, 0.54), one-sided log-rank  $p < 0.0001$ ]. The results of the PFS analysis based on independent central radiological assessment were consistent with the investigator assessment. PFS results were also consistent across the subgroups of age, race, presence and extent of visceral metastases, and sensitivity to prior hormonal therapy.



## **Advanced Neuroendocrine Tumors**

### ***Locally Advanced or Metastatic Advanced Pancreatic Neuroendocrine Tumors (PNET)***

A randomized, double-blind, multi-center trial (RADIANT-3, NCT00510068) of AFINITOR plus best supportive care (BSC) versus placebo plus BSC was conducted in 510 patients with locally advanced or metastatic advanced pancreatic neuroendocrine tumors (PNET) and disease progression within the prior 12 months. Patients were stratified by prior cytotoxic chemotherapy (yes versus no) and by WHO performance status (0 versus 1 and 2). The primary endpoint for the trial was progression-free survival (PFS) evaluated by RECIST (Response Evaluation Criteria in Solid Tumors). The trial demonstrated a statistically significant improvement in PFS (median 11.0 months versus 4.6 months), resulting in a 65% risk reduction in investigator-determined PFS (HR 0.35; 95% CI: 0.27 to 0.45;  $p < 0.001$ ). PFS improvement was observed across all patient subgroups, irrespective of prior somatostatin analog use.

### ***Unresectable, Locally Advanced or Metastatic, Well-Differentiated, Non-Functional Neuroendocrine Tumors of Gastrointestinal or Lung Origin***

A randomized, double-blind, multicenter study (RADIANT-4, NCT01524783) of AFINITOR plus best supportive care (BSC) versus placebo plus best supportive care was conducted in patients with unresectable, locally advanced or metastatic, well differentiated, non-functional neuroendocrine tumors (NET) of gastrointestinal (excluding pancreatic) or lung origin. The study required that patients had well-differentiated (low or intermediate grade) histology, no prior or current history of carcinoid symptoms, and evidence of disease progression within 6 months prior to randomization. A total of 302 patients were randomized 2:1 to receive Afinitor 10 mg/day or placebo, and stratified by prior somatostatin analog (SSA) use (yes versus no), tumor origin and WHO performance status (0 versus 1). The major efficacy outcome measure was progression-free survival (PFS) based on independent radiological assessment evaluated by RECIST. The study demonstrated a statistically significant improvement in PFS per independent radiological review [HR 0.48 (95% CI: 0.35, 0.67),  $p < 0.001$ ].

## **Advanced Renal Cell Carcinoma**

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 and sixteen patients were randomized 2:1 to treatment with everolimus 10 mg daily or





placebo orally in combination with best supportive care. Median PFS was 4.9 months (95% CI 4.0–5.5) for the everolimus-treated group vs. 1.9 months (1.8–1.9) for the placebo-treated group [HR 0.33, (95% CI: 0.25 to 0.43),  $p < 0.0001$ ] by independent central review

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.

Everolimus was compared to nivolumab, a programmed death 1 (PD-1) checkpoint inhibitor, and cabozantinib, an oral TKI active against multiple receptor tyrosine kinases, in treating advanced clear cell carcinoma previously treated with anti-angiogenic therapy. Everolimus was weaker in efficacy vs. both. However, since these two phase 3 trials were open-label, they did not offer the highest level of evidence.

Everolimus was the active comparator against nivolumab in previously treated, advanced renal cell carcinoma in a randomized, open-label, phase III trial (CheckMate 025) involving 821 patients. The median overall survival (OS) was 26.0 months for the group receiving nivolumab 3 mg/kg IV every 2 weeks and 19.7 months for the group taking everolimus 10 mg oral tablet once daily [HR 0.73, (95% CI: 0.61 – 0.88),  $p = 0.0006$ ]. The objective response rate (ORR) was 26% for the nivolumab arm vs 5% for the everolimus arm [odds ratio 6.13, (95% CI: 3.77 – 9.95)].

Everolimus was the active comparator against cabozantinib in a randomized, open-label, phase III trial (METEOR) involving 658 patients. Median overall survival was 21.4 months (95% CI: 18.7 – not estimable) in the cabozantinib arm and 16.5 months (95% CI: 14.7 – 18.8) with everolimus [HR 0.66, (95% CI 0.53-0.83),  $p = 0.00026$ ]. Cabozantinib also had superior PFS [HR 0.51, (95% CI: 0.41-0.62),  $p < 0.0001$ ].



### **Renal Angiomyolipoma with Tuberous Sclerosis Complex**

A randomized (2:1), double-blind, placebo-controlled trial (EXIST-2, NCT00790400) of AFINITOR was conducted in 118 patients with renal angiomyolipoma as a feature of TSC (n=113) or sporadic lymphangiomyomatosis (n=5). The major efficacy outcome measure was angiomyolipoma response rate based on independent central radiology review. There were 33 (41.8%) patients with angiomyolipoma responses in the AFINITOR arm as compared to none in the placebo arm.

### **Subependymal Giant Cell Astrocytoma with Tuberous Sclerosis Complex**

A randomized (2:1), double-blind, placebo-controlled trial (EXIST-1, NCT00789828) of AFINITOR was conducted in 117 pediatric and adult patients with subependymal giant cell astrocytoma (SEGA) and tuberous sclerosis complex (TSC). The main efficacy outcome measure was SEGA response rate based on independent central radiology review. There were 27 (35%) patients with SEGA responses in the AFINITOR arm and no SEGA responses in the placebo arm.

### **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- $\alpha$  to those receiving Torisel or Torisel plus IFN- $\alpha$ . 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- $\alpha$  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- $\alpha$ . The combination of Torisel 15 mg and IFN- $\alpha$  did not result in a significant increase in overall survival when compared with IFN- $\alpha$  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*

### **Afinitor® (everolimus)**

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 non-infectious pneumonitis, which was reported in up to 19% of patients treated with Afinitor® (everolimus) in clinical trials. Grade 3 and 4 non-infectious pneumonitis was up to 4.0% and 0.2% respectively. Physicians and patients should also be aware of the increased risk of infections with everolimus therapy. Patients taking concomitant ACE inhibitor therapy may be at risk for developing angioedema (6.8% vs. 1.3% in control arm). Stomatitis, including mouth ulcers and oral mucositis, has occurred in patients treated with Afinitor® (everolimus) at an incidence ranging from 44%-78% across the clinical trial experience. Grade 3 or 4 stomatitis was reported in 4%-9% of patients. Everolimus delays wound healing and increases the occurrence of wound-related complications, which may require surgical intervention. Cases of renal failure and related fatality have been reported in patients treated with Afinitor® (everolimus). Inhibition of mTOR-regulated glucose and lipid metabolism may result in hyperglycemia, hypertriglyceridemia, and hyperlipidemia. Other laboratory abnormalities often seen with everolimus treatment include elevated LFT, hypokalemia, hypophosphatemia, anemia, leukopenia, and thrombocytopenia.

The most commonly reported (observed at an incidence  $\geq 30\%$ ) 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  $\geq 50\%$ ) include anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine.

The most common grade 3/4 toxicities (incidence  $\geq 3\%$ ) are infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common grade 3/4 laboratory abnormalities (incidence  $\geq 3\%$ ) are lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Grade 3/4 aggression and agitation was reported in 5% of everolimus-treated patients (vs. 0% in placebo) in the EXIST-1 trial involving younger patients (median age 9.5 years).

### **Torisel® (temsirolimus)**

Hypersensitivity/infusion reactions, including but not limited to flushing, chest pain, and anaphylaxis etc, have been associated with the administration of temsirolimus. In a phase 3 trial, 89% of patients receiving TORISEL had at least one elevated serum glucose while on treatment, and 26% of patients reported hyperglycemia as an adverse event. Patients treated with temsirolimus are at risk for immunosuppression and opportunistic infections. Other severe adverse events associated with temsirolimus include hyperlipidemia, bowel perforation, interstitial lung disease, intracerebral hemorrhage, abnormal wound healing, renal failure, proteinuria, and nephrotic syndrome. The most common ( $\geq 30\%$ ) adverse reactions observed with temsirolimus are rash, asthenia, mucositis, nausea, edema, and anorexia. The most common ( $\geq 30\%$ ) laboratory abnormalities observed with temsirolimus are anemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, lymphopenia, elevated alkaline phosphatase, elevated serum creatinine, hypophosphatemia, thrombocytopenia, elevated AST, and leukopenia.

### **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 / lymphangioliomyomatosis, 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.

## 2018 Update

Afinitor Disperz (everolimus tablets for oral suspension) was added. Updated per literature search from 1/1/17 to 4/1/18 and label changes.

## References

---

1. Brown EJ, Albers MW, Shin TB, Ichikawa K, Keith CT, Lane WS, Schreiber SL (June 1994). "A mammalian protein targeted by G1-arresting rapamycin-receptor complex". *Nature* 369 (6483): 756–8.
2. Moore PA, Rosen CA, Carter KC (April 1996). "Assignment of the human FKBP12-rapamycin-associated protein (FRAP) gene to chromosome 1p36 by fluorescence in situ hybridization". *Genomics* 33 (2): 331–2.
3. Hay N, Sonenberg N (2004). "Upstream and downstream of mTOR". *I* 18 (16):1926–45.
4. Beevers C, Li F, Liu L, Huang S (2006). "Curcumin inhibits the mammalian target of rapamycin-mediated signaling pathways in cancer cells" *Int J Cancer* 119 (4):757–64.
5. Afinitor prescribing information. Novartis Pharmaceuticals. East Hanover, NJ. March 2009.
6. Torisel prescribing information. Wyeth Pharmaceuticals, Inc. Philadelphia, PA. September 2010.
7. Mita MM, Mita A, Rowinsky EK. The molecular target of rapamycin (mTOR) as a therapeutic target against cancer. *Cancer Biol Ther.* 2003; 2(4 Suppl 1):S169-S177.
8. Wouters BG, Koritzinsky M. Hypoxia signaling through mTOR and the unfolded protein response in cancer. *Nat Rev Cancer.* 2008; 8(11):851-64.
9. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Kidney Cancer. V.2.2011. Available at: [http://www.nccn.org/professionals/physician\\_gls/pdf/kidney.pdf](http://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf) Accessed May 2018.
10. Motzer RJ, Escudier BJ, Oudard S, et al for the RECORD-1 Study Group. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised placebo-controlled phase III trial. *Lancet.* 2008;372:449-456.



11. Hudes G, Carducci M, Tomczak P et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med*. 2007;356(22):2271-2281.
12. Amato RJ, Jac J, Giessinger S et al. 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*. 2009;115:2438-2446.
13. Whorf RC, Hainsworth JD, Spigel DR et al. A phase II study of bevacizumab and everolimus (RAD001) in the treatment of advanced renal cell carcinoma (RCC). *J Clin Oncol* 2008; 26(15S): Abstract 5010.
14. National Cancer Institute (NCI). SEER stat fact sheets. Cancer: kidney and renal pelvis. Available at <http://seer.cancer.gov/statfacts/html/kidrp.html> Accessed May 2018.
15. Shah S. Renal cancer. In: Richardson M, Chan C, Cheng JWM, et al, eds. *Pharmacotherapy Self-Assessment Program*, 6th ed. Book 10: Oncology. Lenexa, KS: American College of Clinical Pharmacy, 2009:73-82.
16. Mita MM, Mita A, Rowinsky EK. The molecular target of rapamycin (mTOR) as a therapeutic target against cancer. *Cancer Biol Ther*. 2003; 2(4 Suppl 1):S169-S177.
17. Wouters BG, Koritzinsky M. Hypoxia signaling through mTOR and the unfolded protein response in cancer. *Nat Rev Cancer*. 2008; 8(11):851-64.
18. National Comprehensive Cancer Network Compendium. Available at: [https://www.nccn.org/professionals/drug\\_compendium/default.aspx](https://www.nccn.org/professionals/drug_compendium/default.aspx) Accessed May 2018.
19. Everolimus: Drug Information. Lexicomp, UpToDate. Uses. 13 Aug 2015. <http://www.uptodate.com/contents/everolimus-patient-drug-information> Accessed May 2018.
20. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2016; 17(7): 917-927
21. Tomita Y, Fukasawa S, Shinohara N, et al. Nivolumab versus everolimus in advanced renal cell carcinoma: Japanese subgroup analysis from the CheckMate 025 study. *Jpn J Clin Oncol*. 2017; 47(7): 639-646.
22. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2015; 373(19): 1803-1813.
23. Ghobrial IM, Gertz M, Laplant B, et al. Phase II trial of the oral mammalian target of rapamycin inhibitor everolimus in relapsed or refractory Waldenström macroglobulinemia. *J Clin Oncol*. 2010; 28: 1408-1414 NCCN Guidelines. Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma (Version 1.2018). [http://www.nccn.org/professionals/physician\\_gls/pdf/waldenstroms.pdf](http://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf) Accessed May 2018.
24. NCCN Guidelines. Breast Cancer (Version 4.2017). Available at: [http://www.nccn.org/professionals/physician\\_gls/pdf/breast\\_blocks.pdf](http://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf). Accessed May 2018.
25. André F, O'Regan R, Ozguroglu M, et al. Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol*. 2014; 15(6): 580-591.
26. Gold Standard, Inc. Everolimus. Clinical Pharmacology [database online]. Available at <http://www.clinicalpharmacology.com>. Accessed April, 2018.
27. NCCN Guidelines. Kidney Cancer (Version 3.2018). [http://www.nccn.org/professionals/physician\\_gls/pdf/kidney\\_blocks.pdf](http://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf) Accessed May 2018.
28. NCCN Guidelines. Thyroid Carcinoma (Version 2.2017). Available at: [http://www.nccn.org/professionals/physician\\_gls/pdf/thyroid\\_blocks.pdf](http://www.nccn.org/professionals/physician_gls/pdf/thyroid_blocks.pdf) Accessed May 2018.
29. NCCN Guidelines. Hodgkin Lymphoma (Version 1.2071). Available at: [http://www.nccn.org/professionals/physician\\_gls/pdf/hodgkin\\_blocks.pdf](http://www.nccn.org/professionals/physician_gls/pdf/hodgkin_blocks.pdf) Accessed May 2018.
30. NCCN Guidelines. Uterine Neoplasms. [http://www.nccn.org/professionals/physician\\_gls/pdf/uterine\\_blocks.pdf](http://www.nccn.org/professionals/physician_gls/pdf/uterine_blocks.pdf). Accessed May 2018.



31. NCCN Guidelines. Soft Tissue Sarcoma (Version 2.2018). Available at: [http://www.nccn.org/professionals/physician\\_gls/pdf/sarcoma\\_blocks.pdf](http://www.nccn.org/professionals/physician_gls/pdf/sarcoma_blocks.pdf) Accessed May 2018.
32. NCCN Guidelines. Bone Cancer (Version 2.2018). Available at: [http://www.nccn.org/professionals/physician\\_gls/pdf/bone\\_blocks.pdf](http://www.nccn.org/professionals/physician_gls/pdf/bone_blocks.pdf) Accessed May 2018.
33. Gold Standard, Inc. Temsirolimus. Clinical Pharmacology [database online]. Available at <http://www.clinicalpharmacology.com> Accessed May 2018.
34. Hess G, Herbrecht R, Romaguera J, et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell carcinoma. *J Clin Oncol.* 2009; 27(23): 3822-3829.

## History

Date	Comments
05/10/11	Add to Prescription Drug Section - New Policy.
01/27/12	HCPCS code J8561 added to policy.
07/20/12	Replace policy. Policy updated with literature review; no change in policy statements. HCPCS codes J7507, J7520 and J9330 added to coding section.
10/14/13	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.
11/10/14	Annual review. Policy updated to include new NCCN recommendations for neuroendocrine tumors and endometrial carcinoma.
09/08/15	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).
10/01/16	Annual review, approved September 13, 2016: Inclusion of a new indication for Afinitor.
06/01/17	Annual Review, approved May 23, 2017. A statement outlining the length of therapy for initial approval has been added to the policy.
11/14/17	Coding updated, removed HCPCS code J8561 and added HCPCS code J7527. Minor formatting updates were made.
06/01/18	Annual Review, approved May 3, 2018. Afinitor Disperz (everolimus tablets for oral suspension) was added. Updated per literature search from 1/1/17 to 4/1/18 and label changes. Removed oral drug HCPCS codes J7507, J7520, and J7527.



**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 and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.





**Discrimination is Against the Law**

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:

- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals  
PO Box 91102, Seattle, WA 98111  
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357  
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at: U.S. Department of Health and Human Services  
200 Independence Avenue SW, Room 509F, HHH Building  
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)  
Complaint forms are available at <http://www.hhs.gov/ocr/office/file/index.html>.

**Getting Help in Other Languages**

**This Notice has Important Information.** This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

**አማርኛ (Amharic):**

ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ Premera Blue Cross ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀዳሾች ሊኖሩ ይችላሉ። የጤና ሽፋንዎን ለመጠበቅና በአስፋፈል እርዳታ ለማግኘት በተውሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎት ይሆናል። ይህን መረጃ እንዲያገኙ እና የለምንም ክፍያ በቋንቋዎ እርዳታ እንዲያገኙ መሰታ አለዎት። በስልክ ቁጥር 800-722-1471 (TTY: 800-842-5357) ይደውሉ።

**العربية (Arabic):**

يحتوي هذا الإشعار على معلومات هامة. قد يحوي هذا الإشعار معلومات مهمة بخصوص طلبك أو التغطية التي تزيد الحصول عليها من خلال Premera Blue Cross. قد تكون هناك تواريخ مهمة في هذا الإشعار. وقد تحتاج لاتخاذ إجراء في تاريخ معينه للحفاظ على تغطيتك الصحية أو المساعدة في دفع التكاليف. يحق لك الحصول على هذه المعلومات والمساعدة بلغتك دون تكبد أية تكلفة. اتصل بـ 800-722-1471 (TTY: 800-842-5357)

**中文 (Chinese):**

**本通知有重要的訊息。**本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

**Oromoo (Cushite):**

**Beeksisni kun odeeffannoo barbaachisaa qaba.** Beeksisti kun sagantaa yookan karaa Premera Blue Cross tiin tajaajila keessan ilaalchisee odeeffannoo barbaachisaa qabaachuu danda'a. Guyyaawwan murteessaa ta'an beeksisa kana keessatti ilaalaa. Tarii kaffaltiidhaan deeggaramuuf yookan tajaajila fayyaa keessaniif guyyaa dhumaa irratti wanti raawwattan jiraachuu danda'a. Kaffaltii irraa bilisa haala ta'een afaan keessaniin odeeffannoo argachuu fi deeggarsa argachuuf mirga ni qabaattu. Lakkoofsa bilbilaa 800-722-1471 (TTY: 800-842-5357) tii bilbilaa.

**Français (French):**

**Cet avis a d'importantes informations.** Cet avis peut avoir d'importantes informations sur votre demande ou la couverture par l'intermédiaire de Premera Blue Cross. Le présent avis peut contenir des dates clés. Vous devez peut-être prendre des mesures par certains délais pour maintenir votre couverture de santé ou d'aide avec les coûts. Vous avez le droit d'obtenir cette information et de l'aide dans votre langue à aucun coût. Appelez le 800-722-1471 (TTY: 800-842-5357).

**Kreyòl ayisyen (Creole):**

**Avi sila a gen Enfòmasyon Enpòtan ladann.** Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kèk aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resewva enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rele nan 800-722-1471 (TTY: 800-842-5357).

**Deutsche (German):**

**Diese Benachrichtigung enthält wichtige Informationen.** Diese Benachrichtigung enthält unter Umständen wichtige Informationen bezüglich Ihres Antrags auf Krankenversicherungsschutz durch Premera Blue Cross. Suchen Sie nach eventuellen wichtigen Terminen in dieser Benachrichtigung. Sie könnten bis zu bestimmten Stichtagen handeln müssen, um Ihren Krankenversicherungsschutz oder Hilfe mit den Kosten zu behalten. Sie haben das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Rufen Sie an unter 800-722-1471 (TTY: 800-842-5357).

**Hmoob (Hmong):**

**Tsawb ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb.** Tej zaum tsawb ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam hnuv ntawm Premera Blue Cross. Tej zaum muaj cov hnuv tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas pab kom koj ua tsis pub dhau cov caij nyoog uas teev tseg rau hauv daim ntawv no mas koj thiaj yuav tau txais kev pab cuam kho mob los yog kev pab them tej nqi kho mob ntawd. Koj muaj cai kom lawv muab cov ntshiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

**Iloko (Ilocano):**

**Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion.** Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyonyo wenno coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a petsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikular a naituding nga aldaw tapno mapagtalinaedyo ti coverage ti salun-ato wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagsasao nga awan ti bayadanyo. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

**Italiano (Italian):**

**Questo avviso contiene informazioni importanti.** Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente. Chiama 800-722-1471 (TTY: 800-842-5357).

**日本語 (Japanese):**

この通知には重要な情報が含まれています。この通知には、Premera Blue Cross の申請または補償範囲に関する重要な情報が含まれている場合があります。この通知に記載されている可能性がある重要な日付をご確認ください。健康保険や有料サポートを維持するには、特定の期日までに行動を取らなければならない場合があります。ご希望の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

**한국어 (Korean):**

본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross 를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 본 통지서에는 핵심이 되는 날짜들이 있을 수 있습니다. 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하의 이러한 정보와 도움을 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357) 로 전화하십시오.

**ລາວ (Lao):**

ແຈ້ງການນີ້ມີຂໍ້ມູນສໍາຄັນ. ແຈ້ງການນີ້ອາດຈະມີຂໍ້ມູນສໍາຄັນກ່ຽວກັບຄໍາຮ້ອງສະໝັກ ຫຼື ຄວາມຄົມຄອງປະກັນໄພຂອງທ່ານຜ່ານ Premera Blue Cross. ອາດຈະມີວັນທີ່ສໍາຄັນໃນແຈ້ງການນີ້. ທ່ານອາດຈະຈຳເປັນຕ້ອງດໍາເນີນການຕາມກຳນົດ ເວລາສະເພາະເພື່ອຮັກສາຄວາມຄົມຄອງປະກັນສະພາບ ຫຼື ຄວາມຊ່ວຍເຫຼືອເວັ້ນເວົ້ອງຄ່າໃຊ້ຈ່າຍຂອງທ່ານໄດ້. ທ່ານມີສິດໄດ້ຮັບຂໍ້ມູນນີ້ ແລະ ຄວາມຊ່ວຍເຫຼືອເປັນພາສາຂອງທ່ານໂດຍບໍ່ເສຍຄ່າ. ໃຫ້ໃບທາ 800-722-1471 (TTY: 800-842-5357).

**ភាសាខ្មែរ (Khmer):**

សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរៀបចំរបស់អ្នកកាមរយ: Premera Blue Cross ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ជាក់សមត្ថភាព ដល់កិច្ចការផ្ទៃក្នុងដូចជា ឆ្លើយតបនូវសំណួរ ឬប្រាកដន្នយុទ្ធសាស្ត្រ។ អ្នកមានសិទ្ធិទទួលបានព័ត៌មាននេះ និងដំណោះស្រាយនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-722-1471 (TTY: 800-842-5357)។

**ਪੰਜਾਬੀ (Punjabi):**

ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ Premera Blue Cross ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ . ਇਸ ਨੋਟਿਸ ਨਵ ਖਾਸ ਤਾਰੀਖਾਂ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀਂ ਜਸਰਤ ਕਵਰੇਜ ਰਿੱਖਣੀ ਹੋਵੇ ਜਾਂ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਛੁੱਕ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ ਤੋਂ ਪਹਿਲਾਂ ਢੁੱਝ ਖਾਸ ਕਦਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫਤ ਵਿੱਚ ਤੋਂ ਅਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-722-1471 (TTY: 800-842-5357).

**فارسی (Farsi):**

این اعلامیه حاوی اطلاعات مهم میباشد. این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق Premera Blue Cross باشد. به تاریخ های مهم در این اعلامیه توجه نمایید. شما ممکن است برای حفظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کارهای خاصی احتیاج داشته باشید. شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-722-1471 (کلیران TTY تماس باشماره 800-842-5357) تماس برقرار نمایید.

**Polskie (Polish):**

To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócić uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-722-1471 (TTY: 800-842-5357).

**Português (Portuguese):**

Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

**Română (Romanian):**

Prezenta notificare conține informații importante. Această notificare poate conține informații importante privind cererea sau acoperirea asigurării dumneavoastră de sănătate prin Premera Blue Cross. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistența provizorie la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-722-1471 (TTY: 800-842-5357).

**Русский (Russian):**

Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

**Fa'asamoa (Samoan):**

Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, Premera Blue Cross, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilo fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'matalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-722-1471 (TTY: 800-842-5357).

**Español (Spanish):**

Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

**Tagalog (Tagalog):**

Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganiitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

**ไทย (Thai):**

ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับกาการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือในภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 800-722-1471 (TTY: 800-842-5357)

**Український (Ukrainian):**

Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страховального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

**Tiếng Việt (Vietnamese):**

Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình Premera Blue Cross. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-722-1471 (TTY: 800-842-5357).