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PHARMACY / MEDICAL POLICY – 5.01.533

mTOR Kinase Inhibitors

Effective Date:	Apr. 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Mar. 24, 2025	None
Replaces:	N/A	

Select a hyperlink below to be directed to that section.

∞ 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

Use of mTOR Kinase Inhibitors in Cancer and Rare Diseases

Drug	Medical Necessity
Oral Drugs	
Generic everolimus tablet (2.5 mg, 5 mg, 7.5 mg, and 10 mg)	**Generic everolimus tablet (2.5 mg, 5 mg, 7.5 mg, and 10 mg) may be considered medically necessary for the 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 • Adults with advanced renal cell carcinoma (RCC) after treatment failure with Sutent (sunitinib) or Nexavar (sorafenib) • Adults with progressive, unresectable neuroendocrine tumors (NET) of pancreatic (PNET), gastrointestinal or lung origin • Adults with renal angiomyolipoma with tuberous sclerosis complex (TSC) not requiring immediate surgery **AND** • The dose is limited to 10 mg per day **Generic everolimus tablet (2.5 mg, 5 mg, 7.5 mg, and 10 mg) may be considered medically necessary for the treatment of:** • Treatment of adult and pediatric individuals aged 1 year and older with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected **Note:** Everolimus is not labeled for use in people with carcinoid tumors that actively produce hormones. NCCN assigns these a Category 2A recommendation.
Afinitor (everolimus tablet)	**Afinitor (everolimus tablet) may be considered medically necessary for the 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 • Adults with advanced renal cell carcinoma (RCC) after treatment failure with Sutent (sunitinib) or Nexavar (sorafenib)

Drug	Medical Necessity
	• Adults with progressive, unresectable neuroendocrine tumors (NET) of pancreatic (PNET), gastrointestinal or lung origin • Adults with renal angiomyolipoma with tuberous sclerosis complex (TSC) not requiring immediate surgery **AND** • The dose is limited to 10 mg per day **AND** • The individual has tried generic everolimus tablet and had an inadequate response or intolerance to generic everolimus tablet **Afinitor (everolimus tablet) may be considered medically necessary for the treatment of:** • Treatment of adult and pediatric individuals aged 1 year and older with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected **AND** • The individual has tried generic everolimus tablet and had an inadequate response or intolerance to generic everolimus tablet **Note:** Everolimus is not labeled for use in people with carcinoid tumors that actively produce hormones. NCCN assigns these a Category 2A recommendation.
Generic everolimus tablet for oral suspension (2 mg, 3 mg, and 5 mg)	**Generic everolimus tablet for oral suspension (2 mg, 3 mg, and 5 mg) may be considered medically necessary for the treatment of:** • Adult and pediatric individuals aged 1 year and older with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected • Adult and pediatric individuals aged 2 years and older with TSC-associated partial-onset seizures

Drug	Medical Necessity
	Note: Everolimus is not labeled for use in people with carcinoid tumors that actively produce hormones. NCCN assigns these a Category 2A recommendation.
Afinitor Disperz (everolimus tablet for oral suspension)	**Afinitor Disperz (everolimus tablet for oral suspension) may be considered medically necessary for the treatment of:** • Adult and pediatric individuals aged 1 year and older with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected • Adult and pediatric individuals aged 2 years and older with TSC-associated partial-onset seizures **AND** • The individual has tried generic everolimus tablet for oral suspension and had an inadequate response or intolerance to generic everolimus tablet for oral suspension **Note:** Everolimus is not labeled for use in people with carcinoid tumors that actively produce hormones. NCCN assigns these a Category 2A recommendation.
Topical Drugs	

Hyftor (sirolimus topical gel)	**Hyftor (sirolimus topical gel) may be considered medically necessary for the treatment of facial angiofibroma associated with tuberous sclerosis complex (TSC) when:**
	• The individual is aged 6 years or older
	AND
	• Has facial angiofibroma associated with TSC
	AND
	• Dose is limited to:
	  ○ 600 mg (2 cm) for individuals 6-11 years of age
	  ○ 800 mg (2.5 cm) for individuals ≥ 12 years of age

Injectable Drugs	
Fyarro (sirolimus protein-bound particles) IV	**Fyarro (sirolimus protein-bound particles) may be considered medically necessary for the treatment of adult individuals with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor (PEComa).**

Drug	Medical Necessity
Torisel (temsirolimus) IV	**Torisel (temsirolimus) may be considered medically necessary for the treatment of individuals with advanced renal cell carcinoma (RCC).**

Use of mTOR Kinase Inhibitors in Organ Transplants

Drug	Medical Necessity
Oral Drugs	
Everolimus tablet (generic; 0.25 mg, 0.5 mg, 0.75 mg, and 1 mg), Zortress (everolimus)	**Everolimus tablet (0.25 mg, 0.5 mg, 0.75 mg, and 1 mg) and Zortress (everolimus) are considered medically necessary for prophylaxis of organ rejection in allogeneic transplant individuals.** **Note:** Everolimus tablet (0.25 mg, 0.5 mg, 0.75 mg, and 1 mg) and Zortress (everolimus) do NOT require a prior authorization.
Prograf (tacrolimus)	**Prograf (tacrolimus) is considered medically necessary for the prophylaxis of organ rejection in individuals receiving allogeneic transplants.** **Note:** This drug does NOT require a prior authorization.
Rapamune (sirolimus)	**Rapamune (sirolimus) is considered medically necessary for:** • Prophylaxis of organ rejection in individuals receiving allogeneic transplants. • Treatment of individuals with lymphangioleiomyomatosis **Note:** This drug does NOT require prior authorization.

Drug	Investigational
As listed	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for all drugs listed in this policy may be approved up to 12 months.** **All other reviews for oral and topically administered drugs listed in this policy may be approved up to 3 months.** **All other reviews for intravenously administered drugs listed in this policy may be approved up to 6 months.**
Re-authorization criteria	**Non-formulary exception reviews and all other reviews for all drugs listed in this policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history

Coding

Code	Description
CPT	
J9330	Injection, Temsirolimus (Torisel), 1 mg
J9331	Injection, sirolimus protein-bound particles, (Fyarro) 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 managed 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 individuals with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.

Afinitor Disperz (everolimus tablet for oral suspension) is indicated for the adjunctive treatment of adult and pediatric individuals aged 2 years and older with TSC-associated partial-onset seizures.

Torisel (temsirolimus) is indicated for the treatment of advanced renal cell carcinoma. Individuals 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 individuals at low-moderate immunologic risk receiving a kidney or liver transplant. Safety and efficacy in kidney transplant individuals at high immunologic risk, pediatric individuals (<18 years), or recipients of transplanted organs other than kidney or liver have not been established. Kidney transplant individuals should start Zortress immediately after transplantation. Zortress should be used in combination with basiliximab, cyclosporine (reduced doses), and corticosteroids in kidney transplant individuals. Liver transplant individuals 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 individuals.

Prograf (tacrolimus) is indicated for the prophylaxis of organ rejection in individuals receiving allogeneic liver, kidney, heart, or lung transplants, in combination with other immunosuppressants. It is recommended that Prograf be used concomitantly with adrenal corticosteroids. Because of the risk of anaphylaxis, Prograf injection should be reserved for individuals 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 individuals may require higher doses to achieve comparable trough concentration. Rapamune (sirolimus) is indicated for the prophylaxis of organ rejection in individuals aged ≥13 years receiving renal transplants. In individuals 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 individuals 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 individuals. Therapeutic drug monitoring is recommended for all individuals.

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 2021, it was estimated approximately 76,080 new cases of RCC would be diagnosed and approximately 13,780 Americans would die of RCC. The age-adjusted incidence of RCC is 16.4 per 100,000 Americans. From 2014 to 2018, the 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 individuals 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.

Advances 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 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-actived kinase).

Everolimus is only indicated for second-line treatment of advanced (Stage IV) RCC after failure with a VEGF-TKI (sorafanib or sunitinib). Currently, adjuvant therapy is not recommended outside of a clinical trial setting for individuals 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 individuals with locally advanced or metastatic advanced pancreatic neuroendocrine tumors (PNET) and disease progression within the prior 12 months. Individuals 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 individual 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 individuals with unresectable, locally advanced or metastatic, well differentiated, non-functional neuroendocrine tumors (NET) of gastrointestinal (excluding pancreatic) or lung origin. The study required that individuals 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 individuals 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 individuals 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 individual populations and methodologies in these trials were significantly different. At baseline, individuals 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 individuals with progressive metastatic clear cell RCC following a VEGF-TKI and efficacy in combination with bevacizumab for individuals 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 tyroskine 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 individuals. 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 individuals. 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 individuals with renal angiomyolipoma as a feature of TSC (n=113) or sporadic lymphangioleiomyomatosis (n=5). The major efficacy outcome measure was angiomyolipoma response rate based on independent central radiology review. There were 33 (41.8%) individuals 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 individuals 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%) individuals 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 individuals 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 individuals receiving IFN-α to those receiving Torisel or Torisel plus IFN-α. Individuals 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).

Individuals 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 individuals. 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 individuals 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.

Fyarro (sirolimus protein-bound particles)

The efficacy of Fyarro was assessed in AMPECT (NCT02494570), a multicenter, single-arm clinical trial in 31 individuals with locally advanced unresectable or metastatic malignant PEComa. Individuals were required to have measurable disease at baseline, centrally confirmed diagnosis by pathology of malignant PEComa, and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1. Individuals with lymphangioleiomyomatosis and prior treatment with a mechanistic target of rapamycin (mTOR) inhibitor were excluded. Individuals received Fyarro at a dose of 100 mg/m2 on Days 1 and 8 of 21-day cycles until disease progression or unacceptable toxicity.

The efficacy population of 31 individuals had the following demographic characteristics: median age 60 years (range 34 to 78), female (81%), White (74%), Black (10%), and ECOG PS of 0 (81%). Five (16%) individuals had locally advanced disease and 26 (84%) had metastatic disease. Ninety four percent of individuals had prior surgery,19% had prior radiation therapy, and 13% had prior systemic therapy. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) as assessed by blinded independent central review (BICR) using RECIST v.1.1. The overall response rate was 39% (22%, 58%).

Facial Angiofibroma Associated with Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder caused by the constitutive activation of mammalian target or rapamycin (mTOR). TSC affects multiple organ systems and has a diverse clinical manifestation, including benign tumors, cognitive disabilities, and behavioral problems. Angiofibromas are the most predominant feature in nearly all individuals with TSC; 75% of angiofibromas cases typically start appearing between the ages of 2 and 5 years. Skin lesions appear as numerous pink to reddish papules or nodules that are

typically located on the cheeks, nose, and chin. In addition, most individuals develop plaques, hypomelanotic macules, ungual fibromas, and/or shagreen patches.

TSC affects approximately 50,000 people in the US and has an estimated incidence rate of between 1/6000 and 1/10,000 live births. No genetic predisposition and variation in prevalence based on sex were observed.

Skin lesions are permanent, causing appearance concerns that can considerably impair individual quality of life. Moreover, lesions appear in frequent occurrence, can bleed spontaneously, become infected, impair function, and cause pain and disfigurement. Often, invasive therapies such as surgery and laser therapy come with a high risk for complications and sequelae. TSC-associated skin lesions have been described by individuals and caregivers as the "most bothersome" aspects of TSC. Evidence of disease burden specific to TCS-associated facial angiofibroma is limited. However, there is published evidence showing that direct costs for individuals with TSC are greater compared to the general population. A 2018 retrospective study of commercial insurance and Medicaid claims (N=2789, 2010–2015 data) showed that healthcare utilization was 2–3x higher and prescription drug utilization was ≥2x higher for individuals with TSC compared with matched controls. Total per-individual per-year direct costs (2017 data) were approximately 4-fold higher for individuals with TSC versus matched controls ($20,586 versus $4,181 for the commercial-insured and $31,496 vs $7,377 for the Medicaid-insured.

Hyftor (sirolimus topical gel)

A double-blind, randomized, placebo-controlled phase 3 trial including 62 Japanese individuals (35 adults and 27 children) evaluated topical sirolimus for the treatment for adults and pediatric individuals ≥6 years of age with facial angiofibroma associated with TSC for 12 weeks. Topical sirolimus was significantly superior to PBO in improving angiofibromas. The response rate of angiofibromas was 60% in the sirolimus group compared to 0 in the PBO group. In the pediatric individual group, response rate concerning the size of angiofibroma was higher than the adult group (85% vs 41%). Response rates increased from week 4 to week 12 and decreased at week 4 of follow-up

A multicenter, open-label, non-randomized, non-placebo extension study including 94 Japanese individuals evaluated long-term treatment with topical sirolimus for adults and pediatrics individuals with angiofibroma associated with TSC. The extension study lasted 136 weeks. The response rate of TSC individuals to topical sirolimus increased rapidly during the first 12 weeks

and continued to increase gradually thereafter to 78.2% at week 52. Size and color of severe angiofibroma were also improved.

Topical sirolimus improved health-related quality of life in individuals with facial angiofibroma associated with TSC. Using the SF-35 questionnaire, the three scale scores associated with mental health were significantly improved compared to before the treatment.

A systematic review with meta-analysis in 2017 investigated the use of mTOR inhibitors, mostly topical sirolimus, in any dermatology diseases. Evidence was identified for topical sirolimus in the treatment of facial angiofibroma linked to TSC.

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 individuals 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 individuals 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 individuals should also be aware of the increased risk of infections with everolimus therapy. Individuals 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 individuals 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 individuals. 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 individuals 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 ≥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. Grade 3/4 aggression and agitation was reported in 5% of everolimus-treated individuals (vs. 0% in placebo) in the EXIST-1 trial involving younger individuals (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 individuals receiving TORISEL had at least one elevated serum glucose while on treatment, and 26% of individuals reported hyperglycemia as an adverse event. Individuals 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 (≥30%) adverse reactions observed with temsirolimus are rash, asthenia, mucositis, nausea, edema, and anorexia. The most common (≥30%) laboratory abnormalities observed with temsirolimus are anemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, lymphopenia, elevated alkaline phosphatase, elevated serum creatinine, hypophosphatemia, thrombocytopenia, elevated AST, and leukopenia.

Fyarro (sirolimus protein-bound particles)

The safety of Fyarro was assessed in a single-arm study (AMPECT). Thirty-four individuals received Fyarro 100 mg/m2 on Days 1 and 8 of 21-day cycles until disease progression or unacceptable toxicity. Among the 34 individuals who received Fyarro, 16 (47%) were exposed for 6 months or longer and 7 (21%) were exposed for greater than 1 year. Serious adverse reactions occurred in 14 (41%) individuals who received Fyarro. Serious adverse reactions in >5% of individuals, including 4 (12%) individuals with infection and 2 (6%) individuals each with abdominal pain, dehydration, and upper gastrointestinal hemorrhage. Fatal adverse reactions

occurred in 1 (2.9%) individual who received Fyarro and experienced upper gastrointestinal hemorrhage. The most common adverse reactions (≥30%) were stomatitis in 27 (79%) individuals, fatigue and rash in 23 (68%) individuals each, infection in 20 (59%) individuals, nausea and edema in 17 (50%) individuals each, diarrhea, musculoskeletal pain and decreased weight in 16 (47%) individuals each, decreased appetite in 15 (44%) individuals, cough in 12 (35%) individuals, and vomiting and dysgeusia in 11 (32%) individuals each. The most common Grade 3 to 4 laboratory abnormalities (≥6%) were decreased lymphocytes in 7 (21%) individuals, increased glucose and decreased potassium in 4 (12%) individuals each, decreased phosphate in 3 (9%) individuals, and decreased hemoglobin and increased lipase in 2 (6%) individuals each.

Hyftor (sirolimus topical gel)

The safety profile of topical sirolimus for is not well established. Overall, topical sirolimus is safe and tolerable. Most side effects were mostly mild or moderate and localized to the skin and no detectable systemic absorption was observed. In the RCT, one individual had two SAEs with sirolimus (acute pancreatitis and gastric hemorrhage). In the open-label extension study, nine cases of SAEs were found (corpus callosotomy, pharyngitis, pneumothorax, wisdom tooth removal, and therapeutic embolism).

The most common AEs reported by ≥1 of individuals treated with topical sirolimus were dry skin (40%), application site reaction (37%), pruritus (17%), acne (7%), acneiform dermatitis (3%), ocular hyperemia (3%), skin hemorrhage (3%), and skin irritation (3%). AEs occurred in a similar frequency in adult and pediatric individuals.

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.

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.

2019 Update

Reviewed prescribing information for all drugs and no new evidence was identified that would require changes to this policy.

2020 Update

Reviewed prescribing information for all drugs. Added generic everolimus tablet to policy with same coverage criteria as Afinitor (everolimus tablet). Separated Afinitor (everolimus tablet) and Afinitor Disperz (everolimus tablet for oral suspension) coverage criteria. Added Length of Approval and Documentation Requirements tables to policy.

2021 Update

Reviewed prescribing information for all drugs and no new evidence was identified that would require changes to this policy.

2022 Update

Reviewed prescribing information for all drugs and researched product availability. Added coverage criteria for generic everolimus tablet for oral suspension (generic of Afinitor Disperz). Updated coverage criteria for Afinitor to require the individual has tried generic everolimus tablet and had an inadequate response or intolerance to generic everolimus tablet. Updated coverage criteria for Afinitor Disperz to require the individual has tried generic everolimus tablet for oral suspension and had an inadequate response or intolerance to generic everolimus tablet for oral suspension.

2023 Update

Reviewed prescribing information for all drugs and no new evidence was identified that would require changes to this policy.

2024 Update

Reviewed prescribing information for all drugs and no new evidence was identified that would require changes to this policy.

2025 Update

Reviewed prescribing information for all drugs. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

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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

Date	Comments
	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 neoendocrine 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.
05/01/19	Annual Review, approved April 18, 2019. No changes to policy statement.
10/01/20	Annual Review, approved September 17, 2020. Added generic everolimus to policy. Placed a quantity limit on generic everolimus and Afinitor (everolimus tablet).
09/01/21	Annual Review, approved August 3, 2021. No changes to policy statement.
02/01/22	Interim Review, approved January 11, 2022. Added coverage criteria for Fyarro (sirolimus protein-bound particles) for the treatment of adult individuals with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor (PEComa). Added HCPCS code J3490 and J3590.
04/01/22	Coding update. Added new HCPC code C9091.
05/01/22	Annual Review, approved April 12, 2022. Added coverage criteria for generic everolimus tablet for oral suspension (generic of Afinitor Disperz). Updated coverage criteria for Afinitor to require the individual has tried generic everolimus tablet and had an inadequate response or intolerance to generic everolimus tablet. Updated coverage criteria for Afinitor Disperz to require the individual has tried generic everolimus tablet for oral suspension and had an inadequate response or intolerance to generic everolimus tablet for oral suspension.
07/01/22	Coding update. Added HCPCS code J9331. Removed HCPCS codes J3490 and J3590.
11/01/22	Interim Review, approved October 11, 2022. Added coverage for Hyftor (sirolimus topical gel) for the treatment of facial angiofibroma associated with TSC. Changed the wording from "patient" to "individual" throughout the policy for standardization.

Date	Comments
07/01/23	Annual Review, approved June 26, 2023. No changes to policy statements. Deleted termed code C9091.
08/01/24	Annual Review, approved July 22, 2024. No changes to policy statements.
04/01/25	Annual Review, approved March 24, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.

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.