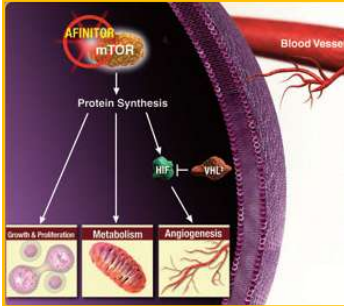


Afinitor[®] (everolimus) Tablets in Advanced Neuroendocrine Tumors (NET) Fact Sheet

<p>About Afinitor & NET</p>	<p>Afinitor[®] (everolimus) tablets is a prescription medicine used to treat adults with a type of pancreatic cancer known as pancreatic neuroendocrine tumors (pNET) that has progressed and cannot be treated with surgery, as well as adults with nonfunctional NET of the stomach and intestine (gastrointestinal, or GI) or the lung that has progressed and cannot be treated with surgery. Afinitor is not for use in people with carcinoid tumors that actively produce hormones.</p> <p>NET are tumors that originate in neuroendocrine cells throughout the body, and most commonly arise in the GI tract, lungs or pancreas^{1,2}. NET can be defined as functional or nonfunctional³. The majority of patients with NET (72%) have nonfunctional NET, which are characterized by symptoms caused by tumor growth^{3,4}. In contrast, functional NET are characterized by symptoms caused by the oversecretion of hormones and other substances³. Five to 44% (depending on site of tumor origin) of patients with GI NET and 28% of patients with lung NET have advanced disease at time of diagnosis, meaning the tumor has spread to other areas of the body. Patients with advanced disease face limited, approved treatment options^{1,2}. Progression, or the continued growth or spread of the tumor, is typically associated with poor prognoses⁵.</p>
<p>How Afinitor Works</p>	<p>Afinitor is an mTOR (mammalian target of rapamycin) inhibitor that can slow the growth and spread of tumors. In vitro and in vivo studies show that Afinitor works by interrupting cellular functions that can stimulate uncontrolled tumor cell growth, creation of new blood vessels and increased cellular metabolism.</p> <p>Afinitor is the first oral targeted agent to demonstrate efficacy and safety across advanced NET arising from the lung, GI tract and pancreas.</p>  <p style="text-align: center;">Tumor Cell</p>
<p>Afinitor NET Registration Trials</p>	<p>The RADIANT (RAD001 In Advanced Neuroendocrine Tumors) program was initiated to evaluate the efficacy and safety of Afinitor in patients with advanced NET. Trials from the RADIANT program, the largest global clinical trial program to be conducted in advanced NET, led to the approval of Afinitor in the NET indications noted above.</p> <p>RADIANT-4: Advanced, Progressive, Well-differentiated, Nonfunctional GI and Lung NET</p> <ul style="list-style-type: none"> • Trial Design: Randomized, double-blind, parallel group, placebo-controlled, multicenter Phase III prospective study of 302 patients with advanced, progressive, well-differentiated (Grade 1 or Grade 2) nonfunctional NET of GI or lung origin and disease progression within the prior 6 months. Patients had no history of and no active symptoms related to carcinoid syndrome and had history of prior somatostatin analogue use. Patients were randomized 2:1 to receive either Afinitor 10 mg daily plus best supportive care (BSC) (n=205) or placebo plus BSC (n=97)⁶ • Primary Endpoint: The primary endpoint was progression-free survival (PFS) based on independent radiological assessment evaluated by Response Evaluation Criteria in Solid Tumors (RECIST)⁶ • Key Results: Afinitor significantly improved PFS, resulting in a 52% risk reduction of progression or death (hazard ratio [HR] = 0.48; 95% confidence interval [CI], 0.35-0.67; p<0.00001) vs placebo. Additionally, data showed Afinitor increased median PFS by 7.1 months: median PFS by central review was 11.0 months (95% CI, 9.2-13.3) in the Afinitor arm and 3.9 months (95% CI, 3.6-7.4) in the placebo arm⁶

	<p>RADIANT-3: Locally Advanced or Metastatic pNET</p> <ul style="list-style-type: none"> • Trial Design: Randomized, double-blind, multicenter Phase III study of 410 patients with well- and moderately differentiated advanced pNET and disease progression within the prior 12 months; patients were randomized 1:1 to receive either Afinitor 10 mg/day plus BSC (n=207) or placebo plus BSC (n=203)⁷ • Primary Endpoint: The primary endpoint was PFS evaluated by RECIST⁷ • Key Results: Afinitor more than doubled (2.4-fold) the prolongation of median PFS (11.0 vs 4.6 months) and reduced the risk of progression or death by 65% vs placebo (HR = 0.35; 95% CI, 0.27-0.45; p<0.0001)⁷
<p>Safety/ Adverse Events</p>	<p>Adverse events (AEs) were similar in the RADIANT-4 and -3 clinical trials and were consistent with the known safety profile of Afinitor.</p> <p>RADIANT-4: The most common treatment-related, all-grade AEs (incidence ≥20%) for Afinitor and placebo, respectively, were stomatitis (inflammation of the mouth or lips; 63% vs 19%), diarrhea (31% vs 16%), fatigue (31% vs 24%), infections (29% vs 4%), rash (27% vs 8%) and peripheral edema (accumulation of fluid causing swelling in lower limbs; 26% vs 4%) The most common treatment-related grade 3/4 AEs (≥5%) for Afinitor and placebo, respectively, were, stomatitis (9% vs 0%), diarrhea (7% vs 2%), infections (7% vs 0%)⁸.</p> <p>RADIANT-3: The most common AEs (≥20%) for Afinitor and placebo, respectively, were stomatitis (64% vs 17%), rash (49% vs 10%), diarrhea (34% vs 10%), fatigue (31% vs 14%), infections (23% vs 6%), nausea (20% vs 18%), peripheral edema (20% vs 3%) and decreased appetite (20% vs 7%). The most common grade 3/4 AEs (≥5%) for Afinitor compared to placebo during the core phase of the study included anemia (6% vs 0%), hyperglycemia (5 % vs 2%) and stomatitis (7% vs 0%)⁷.</p>

About Afinitor[®] (everolimus) tablets

Afinitor[®] (everolimus) tablets is approved in more than 110 countries, including the US and in the European Union, for locally advanced, metastatic or unresectable progressive NET of pancreatic origin. Afinitor is not indicated for the treatment of patients with functional carcinoid tumors in the US. Afinitor is now also approved in the US and EU for the treatment of adult patients with progressive, well-differentiated (Grade 1 or Grade 2), nonfunctional NET of gastrointestinal or lung origin that are unresectable, locally advanced or metastatic.

It is also approved in more than 120 countries including the US and European Union for advanced renal cell carcinoma following progression on or after vascular endothelial growth factor (VEGF)-targeted therapy (in the US, specifically following sunitinib and sorafenib).

Additionally, Afinitor is approved in more than 110 countries including the United States and European Union for advanced HR+/HER2- breast cancer in combination with exemestane, after prior endocrine therapy.

Everolimus is also available from Novartis for use in certain non-oncology patient populations under the brand names Afinitor[®] or Votubia[®], Certican[®] and Zortress[®] and is exclusively licensed to Abbott and sublicensed to Boston Scientific for use in drug-eluting stents.

Indications vary by country and not all indications are available in every country. The safety and efficacy profile of everolimus has not yet been established outside the approved indications. Because of the uncertainty of clinical trials, there is no guarantee that everolimus will become commercially available for additional indications anywhere else in the world.

Important Safety Information about Afinitor[®] (everolimus) tablets

Afinitor/Votubia can cause serious side effects including lung or breathing problems, infections (including sepsis), and kidney failure, which can lead to death. Patients taking concomitant angiotensin-converting enzyme (ACE) inhibitors may be at an increased risk for angioedema. Mouth ulcers and mouth sores are common side effects. Afinitor/Votubia can affect blood cell counts, kidney and liver function, and blood sugar, cholesterol, and triglyceride levels. Afinitor/Votubia may cause fetal harm in pregnant women. Highly effective contraception is recommended for women of

child-bearing potential while receiving Afinitor/Votubia and for up to eight weeks after ending treatment. Women taking Afinitor/Votubia should not breast feed. Fertility in women and men may be affected by treatment with Afinitor/Votubia.

The most common adverse drug reactions (incidence ≥ 10 percent) are infections (including sore throat and runny nose, upper respiratory tract infection, pneumonia, sinusitis, and urinary tract infection), mouth ulcers, skin rash, feeling tired, diarrhea, fever, vomiting, nausea, cough, decreased appetite, low level of red blood cells, headache, abnormal taste, absence of menstrual periods, acne, inflammation of lung tissue, irregular menstrual periods, swelling of extremities or other parts of the body, high level of blood sugar, feeling weak, itching, weight loss, high levels of cholesterol, and nose bleeds. The most common Grade 3-4 adverse drug reactions (incidence ≥ 2 percent) are mouth ulcers, infections (including pneumonia), low level of red blood cells, high level of blood sugar, feeling tired, absence of menstrual periods, diarrhea, low white blood cells, inflammation of lung tissue, feeling weak, fever, and spontaneous bleeding or bruising. Cases of hepatitis B reactivation, blood clots in the lung or legs, and pneumocystis jirovecii pneumonia (PJP) have been reported. Abnormalities were observed in hematology and clinical chemistry laboratory tests.

Please see full Prescribing Information for Afinitor available at www.Afinitor.com.

The brands listed are the trademarks or register marks of their respective owners and are not trademarks or register marks of Novartis.

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