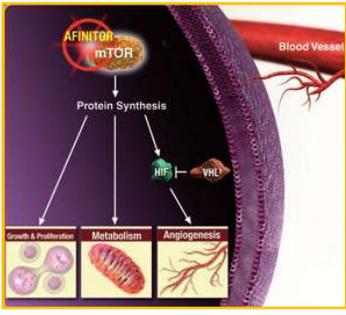


## Fact Sheet on Afinitor<sup>®</sup> (everolimus) tablets in Advanced Neuroendocrine Tumors (NET)

<p><b>About Afinitor &amp; NET</b></p>	<p>Afinitor<sup>®</sup> (everolimus) tablets is a prescription medicine used to treat adults with a type of pancreatic cancer known as pancreatic neuroendocrine tumor (pNET) that has progressed and cannot be treated with surgery, and adults with a type of cancer known as NET of the stomach and intestine (gastrointestinal) 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 a rare type of cancer that originate in neuroendocrine cells throughout the body, and are most often found in the GI tract, lungs or pancreas<sup>1,2</sup>. NET can be defined as functional or nonfunctional. Functional NET are characterized by symptoms caused by the oversecretion of hormones and other substances<sup>3</sup>. Nonfunctional NET may be characterized by symptoms caused by tumor growth<sup>3,4</sup>. NET are often diagnosed at an advanced stage because they tend to grow slowly and cause no symptoms or vague symptoms that can be mistaken for other conditions<sup>1</sup>.</p>
<p><b>How Afinitor Works</b></p>	<p>Afinitor is an mTOR (mammalian target of rapamycin) inhibitor that can slow the growth and spread of tumors. In vitro/in vivo studies show that Afinitor works by interrupting cellular functions that can stimulate uncontrolled cancer cell growth, creation of new blood vessels and increased cellular metabolism.</p> <p>Afinitor is the first targeted agent to demonstrate efficacy and safety across advanced NET arising from the lung, GI tract and pancreas.</p> <div data-bbox="1112 787 1458 1102" data-label="Diagram">  <p>The diagram illustrates the mTOR signaling pathway in a tumor cell. At the top, 'AFINITOR' is shown inhibiting 'mTOR'. This inhibition leads to a decrease in 'Protein Synthesis', which in turn affects three cellular processes: 'Growth &amp; Proliferation', 'Metabolism', and 'Angiogenesis'. Additionally, 'HIF-1' and 'VEGF' are shown as part of the pathway, with HIF-1 inhibiting VEGF, which then promotes angiogenesis. A 'Blood Vessel' is shown on the right, with new vessels forming from the tumor cell.</p> </div> <p style="text-align: center;"><b>Tumor Cell</b></p>
<p><b>Afinitor NET Registration Trials</b></p>	<p>The RADIANT (<b>RA</b>D001 <b>I</b>n <b>A</b>dvanced <b>N</b>euroendocrine <b>T</b>umors) 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 program to be conducted in advanced NET, led to the approval of Afinitor in the NET indications noted above.</p> <p><b>RADIANT-4: Progressive, Nonfunctional GI and Lung NET</b></p> <ul style="list-style-type: none"> <li><b>Trial Design:</b> Randomized, double-blind, multicenter Phase III study of 302 patients (median age 63 years) with unresectable, progressive, well-differentiated, nonfunctional, locally advanced or metastatic NET of GI (excluding pancreatic) or lung origin. 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)</li> <li><b>Primary &amp; Secondary Endpoints:</b> The primary endpoint was progression-free survival (PFS) based on independent radiological assessment evaluated by Response Evaluation Criteria in Solid Tumors (RECIST); key secondary endpoints included overall survival (OS) and best overall response rate (defined as complete response plus partial response)</li> <li><b>Key Results:</b> Afinitor significantly improved PFS, resulting in a 52% risk reduction of progression (hazard ratio [HR] = 0.48; 95% confidence interval [CI], 0.35-0.67; p&lt;0.001) vs placebo. Data also showed Afinitor extended 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 arm</li> </ul> <p><b>RADIANT-3: Locally Advanced or Metastatic pNET</b></p> <ul style="list-style-type: none"> <li><b>Trial Design:</b> Randomized, double-blind, multicenter Phase III study of 410 patients (median age 58 years) with locally advanced or metastatic 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)</li> </ul>

	<ul style="list-style-type: none"> <li>• <b>Primary &amp; Secondary Endpoints:</b> The primary endpoint was PFS evaluated by RECIST; key secondary endpoints included safety, objective response rate (complete response or partial response), response duration and OS</li> <li>• <b>Key Results:</b> Afinitor more than doubled the time without tumor growth (median PFS 11.0 vs 4.6 months) and reduced the risk of cancer progression by 65% vs placebo (HR = 0.35; 95% CI, 0.27-0.45; p&lt;0.001)<sup>5</sup></li> </ul>
<p><b>Safety/ Adverse Events</b></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><b>RADIANT-4:</b> The most common treatment-related, all-grade AEs (incidence ≥30%) included stomatitis (63%), infections (58%), diarrhea (41%), peripheral edema (accumulation of fluid causing swelling in lower limbs) 39%, fatigue (37%) and rash (30%). The most common treatment-related grade 3/4 AEs (≥5%) for Afinitor and placebo, respectively, were infections (11.0% vs 2.0%), diarrhea (9.0% vs 2.0%), stomatitis (9.0% vs 0.0%), fatigue (5.0% vs 1.0%) and hyperglycemia (5.0% vs 0.0%)</p> <p><b>RADIANT-3:</b> The most common AEs (≥30%) were stomatitis (70%), rash (59%), diarrhea (50%), fatigue (45%), edema (39%), abdominal pain (36%), nausea (32%), fever (31%), headache (30%) and decreased appetite (30%). The most common grade 3/4 AEs (≥5%) for Afinitor compared to placebo during the core phase of the study included stomatitis (7.0% vs 0.0%) and diarrhea (5.5% vs 3.0%)<sup>5</sup></p>

**About Afinitor® (everolimus) tablets**

Afinitor® (everolimus) tablets is a prescription medicine used to treat adults with a type of pancreatic cancer known as pancreatic neuroendocrine tumor (pNET) that has progressed and cannot be treated with surgery, and adults with a type of cancer known as NET of the gastrointestinal (GI) or lung origin that has progressed and cannot be treated with surgery. Afinitor is not for use in people with carcinoid tumors that actively produce hormones.

**Important Safety Information**

Patients should not take Afinitor if they are allergic to Afinitor or to any of its ingredients. Patients should tell their health care provider before taking Afinitor if they are allergic to sirolimus (Rapamune®) or temsirolimus (Torisel®).

Afinitor can cause serious side effects, including lung or breathing problems, infections, and kidney failure, which can even lead to death. If patients experience these side effects, they may need to stop taking Afinitor for a while or use a lower dose. Patients should follow their health care provider’s instructions.

In some patients, lung or breathing problems may be severe and can even lead to death. Patients should tell their health care provider right away if they have any of these symptoms: new or worsening cough, shortness of breath, chest pain, difficulty breathing, or wheezing.

Afinitor may make patients more likely to develop an infection, such as pneumonia, or a bacterial, fungal, or viral infection. Viral infections may include reactivation of hepatitis B in people who have had hepatitis B in the past. In some people these infections may be severe and can even lead to death. Patients may need to be treated as soon as possible. Patients should tell their health care provider right away if they have a temperature of 100.5°F or above, chills, or do not feel well. Symptoms of hepatitis B or infection may include the following: fever, chills, skin rash, joint pain and inflammation, tiredness, loss of appetite, nausea, pale stools or dark urine, yellowing of the skin, or pain in the upper right side of the stomach.

Patients who take an angiotensin-converting enzyme (ACE) inhibitor medicine during treatment with Afinitor are at a possible increased risk for a type of allergic reaction called angioedema. Patients should get medical help right away if they have trouble breathing or develop swelling of the tongue, mouth, or throat during treatment with Afinitor.

Afinitor may cause kidney failure. In some people this may be severe and can even lead to death. Patients should have tests to check their kidney function before and during their treatment with Afinitor.



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Afinitor can cause incisions to heal slowly or not heal well. Patients should tell their health care provider if their incision is red, warm, or painful; if they have blood, fluid, or pus in their incision; or if their incision opens up or is swollen.

Common side effects include mouth ulcers and sores. Other common side effects include infections, diarrhea, swelling of the arms, hands, feet, ankles, or other parts of the body, feeling weak or tired, rash, abdominal pain, headache, dry skin, itching, vomiting, cough, shortness of breath, nausea, fever, nose bleed, weight loss, or loss of appetite.

**Please see full Prescribing Information for Afinitor available at [www.Afinitor.com](http://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.

### References

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4. Modlin I, et al. Priorities for improving the management of gastroenteropancreatic neuroendocrine tumors. *J Natl Cancer Inst*. 2008;100:1282-1289.
5. Afinitor (everolimus) Prescribing information. East Hanover, New Jersey, USA: Novartis Pharmaceuticals Corporation; February 2016.

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