

AFINITOR® (everolimus) tablets

Afinitor has been approved by the US Food and Drug Administration (FDA) for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of treatment with Sutent® (sunitinib)* or Nexavar® (sorafenib)*. Novartis has also filed regulatory submissions in the European Union, Switzerland and Japan, as well as with other regulatory agencies globally.

In cancer cells, Afinitor provides continuous inhibition of mTOR, a protein that acts as a central regulator of tumor cell division, blood vessel growth and cell metabolism. Afinitor is being studied in multiple cancer types, including neuroendocrine, breast, gastric and hepatocellular carcinoma (HCC), as well as tuberous sclerosis complex (TSC) and non-Hodgkin's lymphoma.

Afinitor is the first oral, daily therapy (5 mg and 10 mg tablets) approved by the FDA for the treatment of patients with advanced RCC, also known as advanced kidney cancer, after failure of treatment with Sutent or Nexavar.

Renal Cell Carcinoma	<ul style="list-style-type: none">• RCC is the most common type of kidney cancer. In RCC, cancer cells develop in the lining of the kidney's tubes and grow into a mass, commonly called a tumor.• Afinitor, previously known as RAD001, was approved by the FDA for the treatment of patients with advanced RCC after failure of treatment with Sutent or Nexavar, and provides an important new treatment option.• The RECORD-1 (REnal Cell cancer treatment with Oral RAD001 given Daily) trial is an international, randomized, double-blind, placebo-controlled, multi-center trial of 416 patients with advanced RCC whose cancer progressed despite prior treatment with sunitinib, sorafenib or both sequentially.• In the trial, prior therapy with bevacizumab, interferon alfa and interleukin-2 was allowed.• RECORD-1 trial findings, upon which the FDA based their approval, demonstrated that Afinitor, when compared to placebo, more than doubled the time without tumor growth or death in patients with advanced kidney cancer (4.9 vs. 1.9 months) and reduced the risk of disease progression or death by 67% (hazard ratio=0.33 with 95% confidence interval 0.25 to 0.43; P<0.0001).
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Afinitor is being studied in the following tumor types:

Neuroendocrine Tumors	<ul style="list-style-type: none">• Neuroendocrine tumors (NET) are a diverse mixture of tumors formed from cells regulating hormonal activity throughout the body. Gastrointestinal NET (commonly referred to as carcinoid tumors) and pancreatic NET (commonly referred to as islet cell tumors) are two forms of NET.• RADIANT-1 (RAD001 In Advanced Neuroendocrine Tumors) is a Phase II international, multi-center, open label study of RAD001 in patients with advanced pancreatic NET who developed progressive disease on or after prior treatment with cytotoxic chemotherapy.• In the RADIANT-1 trial, patients were given either daily RAD001 combined with monthly Sandostatin LAR® Depot (octreotide acetate for injectable suspension)* or daily RAD001 alone. The results showed that 82% (37 out of 45 patients) of patients receiving combination therapy and 77% (88 out of 115 patients) receiving monotherapy had tumors that did not progress or that remained stable.• Two Phase III trials investigating the use of RAD001 are underway in patients with pancreatic NET and gastrointestinal NET.
Breast Cancer	<ul style="list-style-type: none">• Breast cancer is cancer of the breast tissue. It is the second leading cause of cancer-related death for women in the US.• Data from two Phase I studies showed that RAD001 may reverse/delay resistance to Herceptin® (trastuzumab)* in women with HER2-positive metastatic breast cancer. Results from the first Phase I trial showed that the combination of RAD001 with Herceptin and weekly Taxol® (paclitaxel)* halted tumor growth in 77% (17 out of 22 patients; complete response/partial response/stable disease ≥16 weeks) of patients with HER2-positive metastatic breast cancer with documented resistance to Herceptin. Results from the second Phase I trial showed promising anticancer activity for RAD001 in combination with Herceptin and Navelbine® (vinorelbine)* in heavily pretreated Herceptin-resistant and taxane-pretreated patients with HER2-positive metastatic breast cancer. In the study, RAD001 in combination with Herceptin and Navelbine halted tumor growth in 62% (21 out of 37 patients) of patients.• Novartis will initiate a worldwide Phase III clinical trial program to further evaluate the potential of RAD001 in combination with Herceptin and chemotherapy in patients with HER2-positive metastatic breast cancer.

Gastric Cancer	<ul style="list-style-type: none">• Gastric cancer, commonly referred to as stomach cancer, was diagnosed in 21,500 Americans in 2008 and claimed the lives of more than 10,000 in the same time period.• Results from a Phase II trial show that RAD001 halted tumor growth in 55% of patients with advanced gastric cancer which had progressed despite one or two previous systemic treatments.• A global Phase III clinical trial program to evaluate the efficacy and safety of RAD001 monotherapy in advanced gastric cancer patients will begin enrollment in 2009.
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The active ingredient in Afinitor is everolimus, which is available in different dosage strengths under the trade name Certican®* for the prevention of organ rejection in heart and kidney transplant recipients. Certican was first approved in the EU in 2003. Certican is not approved for use in the US.

Important safety information

Afinitor is contraindicated in patients with hypersensitivity to everolimus, to other rapamycin derivatives or to any of the excipients. Potentially serious adverse reactions include non-infectious pneumonitis and infections for which patients should be monitored carefully and treated as needed. In addition, non-infectious pneumonitis may require temporary dose reduction and/or interruption or discontinuation. Patients with systemic invasive fungal infections should not receive Afinitor. Oral ulceration is a common side effect with Afinitor. Renal function, blood glucose, lipids and hematological parameters should be evaluated prior to the start of therapy with Afinitor and periodically thereafter. Strong or moderate CYP3A4 or P-glycoprotein inhibitors should be avoided. An increase in the dose of Afinitor is recommended when co-administered with a strong CYP3A4 inducer. Live vaccinations and close contact with those who have received live vaccines should be avoided. Afinitor should not be used in patients with severe hepatic impairment. Afinitor may cause fetal harm in pregnant women.

The most common adverse reactions (incidence $\geq 30\%$) were stomatitis, infections, asthenia, fatigue, cough and diarrhea. The most common grade 3/4 adverse reactions (incidence $\geq 3\%$) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain and asthenia. The most common laboratory abnormalities (incidence $\geq 50\%$) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia and increased creatinine. The most common grade 3/4 laboratory abnormalities (incidence $\geq 3\%$) were lymphopenia, hyperglycemia, anemia, hypophosphatemia and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%) and acute renal failure (0.4%) were observed for patients receiving Afinitor.

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* Sutent® is a registered trademark of Pfizer Inc. Nexavar® is a registered trademark of Bayer HealthCare Pharmaceuticals, Inc. and Onyx Pharmaceuticals. Herceptin® is a registered trademark of Genentech, Inc. and Roche. Taxol® is a registered trademark of Bristol-Myers Squibb Company. Navelbine® is a registered trademark of Pierre Fabre Pharmaceuticals, Inc. Certican® and Sandostatin LAR® Depot are registered trademarks of Novartis.