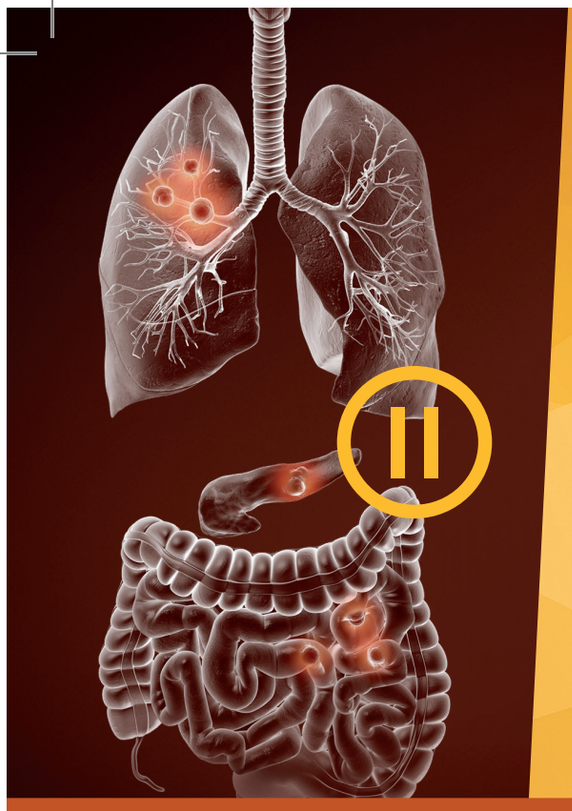


AFINITOR®
(everolimus) tablets
2.5mg | 5mg | 7.5mg | 10mg

SEE NET PROGRESSION?

THINK AFINITOR for your adult patients with progressive PNET and progressive, well-differentiated, nonfunctional GI or lung NET with unresectable, locally advanced, or metastatic disease

Treatment with AFINITOR® (everolimus) Tablets can be considered at the first sign of progression[1]

Median PFS was 11.0 months (95% CI, 8.4-13.9) for AFINITOR vs 4.6 months (95% CI, 3.1-5.4) for placebo (HR=0.35 [95% CI, 0.27-0.45], *P*<0.001) in PNET.[1]
Median PFS was 11.0 months [95% CI, 9.2-13.3] for AFINITOR vs 3.9 months [95% CI, 3.6-7.4] for placebo (HR=0.48 [95% CI, 0.35-0.67], *P*<0.001) in GI and lung NET.[1]

INDICATIONS

AFINITOR® (everolimus) Tablets is indicated for the treatment of adults with progressive neuroendocrine tumors of pancreatic origin (PNET) with unresectable, locally advanced, or metastatic disease.

AFINITOR is indicated for the treatment of adults with progressive, well-differentiated, nonfunctional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin with unresectable, locally advanced, or metastatic disease.

AFINITOR is not indicated for the treatment of patients with functional carcinoid tumors.

IMPORTANT SAFETY INFORMATION

AFINITOR is contraindicated in patients with hypersensitivity to everolimus, to other rapamycin derivatives, or to any of the excipients.

Noninfectious Pneumonitis: Noninfectious pneumonitis was reported in up to 19% of patients treated with AFINITOR; some cases reported with pulmonary hypertension (including pulmonary arterial hypertension) as a secondary event. The incidence of Common Terminology Criteria (CTC) grade 3 and 4 noninfectious pneumonitis was up to 4.0% and up to 0.2%, respectively. Fatal outcomes have been observed. Monitor for clinical symptoms or radiological changes. Opportunistic infections such as *Pneumocystis jiroveci* pneumonia (PJP) should be considered in the differential diagnosis. Manage noninfectious pneumonitis by dose interruption until symptoms resolve, follow with a dose reduction, and consider the use of corticosteroids. Discontinue AFINITOR if toxicity recurs at grade 3 or for grade 4 cases. For patients who require use of corticosteroids, prophylaxis for PJP may be considered. The development of pneumonitis has been reported even at a reduced dose.

Infections: AFINITOR has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoal infections (including those with opportunistic pathogens). Localized and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections; invasive fungal infections, such as aspergillosis, candidiasis, or PJP; and viral infections, including reactivation of hepatitis B virus, have occurred. Some of these infections have been severe (eg, leading to sepsis, respiratory failure, or hepatic failure) or fatal. Physicians and patients should be aware of the increased risk of infection with AFINITOR. Treatment of preexisting invasive fungal infections should be completed prior to starting treatment with AFINITOR. Be vigilant for signs and symptoms of infection and institute appropriate treatment promptly; interruption or discontinuation of AFINITOR should be considered. Discontinue AFINITOR if invasive systemic fungal infection is diagnosed and institute appropriate antifungal treatment.

PJP has been reported in patients who received everolimus, sometimes with a fatal outcome. This may be associated with concomitant use of corticosteroids or other immunosuppressive agents; consider prophylaxis for PJP when concomitant use of these agents is required.

Angioedema With Concomitant Use of Angiotensin-Converting Enzyme (ACE) Inhibitors: Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema (eg, swelling of the airways or tongue, with or without respiratory impairment). In a pooled analysis, the incidence of angioedema in patients taking everolimus with an ACE inhibitor was 6.8% compared to 1.3% in the control arm with an ACE inhibitor.

Please see additional Important Safety Information throughout.
Please see accompanying full Prescribing Information.

Incidence of NET has increased more than 6-fold in nearly 40 years[2]

Incidence of NET is rising faster than the incidence of all malignant tumors

Incidence rate of all malignant neoplasms

13.5%
increase in nearly 40 years*

Incidence rate of NET

540%
increase in nearly 40 years†

*1973 incidence: ~386/100,000; 2012 incidence: ~438/100,000.
†1973 incidence: 1.09/100,000; 2012 incidence: 6.98/100,000.

IMPORTANT SAFETY INFORMATION (continued)

Stomatitis: Stomatitis, including mouth ulcers and oral mucositis, has occurred in patients treated with AFINITOR® (everolimus) Tablets at an incidence ranging from 44% to 78% across the clinical trial experience. Grade 3/4 stomatitis was reported in 4% to 9% of patients. Stomatitis most often occurs within the first 8 weeks of treatment. When starting AFINITOR, initiating dexamethasone alcohol-free oral solution as a swish and spit mouthwash reduces the incidence and severity of stomatitis. If stomatitis does occur, mouthwashes and/or other topical treatments are recommended, but alcohol-, hydrogen peroxide-, iodine-, or thyme-containing products should be avoided. Antifungal agents should not be used unless fungal infection has been diagnosed.

Renal Failure: Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with AFINITOR.

Impaired Wound Healing: Everolimus delays wound healing and increases the occurrence of wound-related complications like wound dehiscence, wound infection, incisional hernia, lymphocele, and seroma. These wound-related complications may require surgical intervention. Exercise caution with the use of AFINITOR in the perisurgical period

Laboratory Tests and Monitoring: Elevations of serum creatinine and proteinuria have been reported. Renal function (including measurement of blood urea nitrogen, urinary protein, or serum creatinine) should be evaluated prior to treatment and periodically thereafter, particularly in patients who have additional risk factors that may further impair renal function.

Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported. Blood glucose and lipids should be evaluated prior to treatment and periodically thereafter. More frequent monitoring is recommended when AFINITOR is coadministered with other drugs that may induce hyperglycemia. Management with appropriate medical therapy is recommended. When possible, optimal glucose and lipid control should be achieved before starting a patient on AFINITOR.

Reductions in hemoglobin, lymphocytes, neutrophils, and platelets have been reported. Monitoring of complete blood count is recommended prior to treatment and periodically thereafter.

Drug-Drug Interactions: Avoid coadministration with strong CYP3A4/PgP inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole). Use caution and reduce the AFINITOR dose to 2.5 mg daily if coadministration with a moderate CYP3A4/PgP inhibitor is required (eg, amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem). Avoid coadministration with strong CYP3A4/PgP inducers (eg, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital); however, if coadministration is required, consider doubling the daily dose of AFINITOR using increments of 5 mg or less.

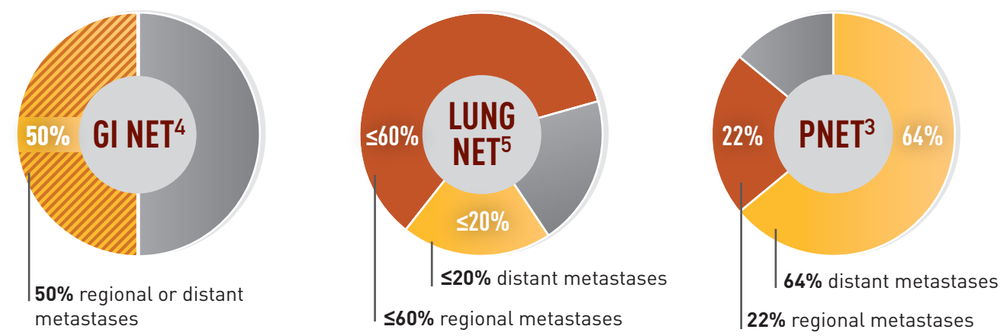
Hepatic Impairment: Exposure to everolimus was increased in patients with hepatic impairment. For patients with severe hepatic impairment (Child-Pugh class C), AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk. For patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, a dose reduction is recommended

Vaccinations: The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with AFINITOR.

Embryo-Fetal Toxicity: Fetal harm can occur if AFINITOR is administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise female patients of reproductive potential to avoid becoming pregnant and to use effective contraception during treatment with AFINITOR and for 8 weeks after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with AFINITOR and for 4 weeks after the last dose.

Up to 86% of patients with NET already have regional or distant metastases at diagnosis[3-5]

Regional and distant metastases in GI NET, lung NET, and PNET



84% of diagnosed NET originate in the GI, lung, or pancreas[3]

Abbreviations: GI, gastrointestinal; NET, neuroendocrine tumors; PNET, pancreatic neuroendocrine tumors.

IMPORTANT SAFETY INFORMATION (continued)

Adverse Reactions in Advanced, Progressive PNET: The most common adverse reactions (incidence ≥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 adverse reactions (incidence ≥5%) were stomatitis (7%) and diarrhea (5.5%). Deaths primarily due to adverse events during the double-blind treatment phase occurred in 7 patients taking AFINITOR.

Laboratory Abnormalities in Advanced, Progressive PNET: The most common laboratory abnormalities (incidence ≥50%, all grades) were: decreased hemoglobin (86%) and bicarbonate (56%); increased fasting glucose (75%), alkaline phosphatase (74%), cholesterol (66%), and aspartate transaminase (56%). The most common grade 3/4 laboratory abnormalities (incidence ≥5%) were: decreased hemoglobin (15%), lymphocytes (16%), and phosphate (10%), and increased glucose (17%) and alkaline phosphatase (8%).

Adverse Reactions in Advanced, Progressive, Well-Differentiated, Nonfunctional GI and Lung NET: The most common adverse reactions (incidence ≥30%) were stomatitis (63%), infections (58%), diarrhea (41%), peripheral edema (39%), fatigue (37%), and rash (30%). The most common grade 3/4 adverse reactions (incidence ≥5%) were infections (11%), stomatitis (9%), diarrhea (9%), fatigue (5%), and hyperglycemia (5%).

References: 1. Afinitor [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2016. **2.** Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States [published online April 27, 2017]. *JAMA Oncol.* 2017:E1-E8. doi:10.1001/jamaoncol.2017.0589. **3.** Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol.* 2008;26(18):3063-3072. **4.** Öberg KE. Gastrointestinal neuroendocrine tumors. *Ann Oncol.* 2010;21(suppl 7):vii72-vii80. **5.** Wolin EM. Challenges in the diagnosis and management of well-differentiated neuroendocrine tumors of the lung (typical and atypical carcinoid): current status and future considerations. *Oncologist.* 2015;20(10):1123-1131. **6.** Yao JC, Fazio N, Singh S, et al; for the RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet.* 2016;387(10022):968-977. **7.** Yao JC, Shah MH, Ito T, et al; RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med.* 2011;364(6):514-523.

Please see additional Important Safety Information throughout.
Please see accompanying full Prescribing Information.

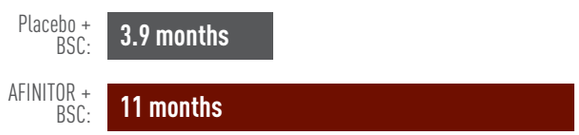
AFINITOR®
(everolimus) tablets
2.5mg | 5mg | 7.5mg | 10mg

For the treatment of adult patients with progressive **PNET** and progressive, well-differentiated, nonfunctional **GI** or **lung NET** with unresectable, locally advanced, or metastatic disease

PRESS PAUSE ON PROGRESSION

Median PFS was more than 2x longer in patients taking AFINITOR® (everolimus) Tablets vs placebo across NET indications[1]*

RADIANT-4 trial for GI and lung NET



- AFINITOR extended median PFS by more than 7 months (HR=0.48 [95% CI, 0.35-0.67], *P*<0.001) vs placebo[1]

RADIANT-3 trial for PNET

- AFINITOR extended median PFS by more than 6 months (HR=0.35 [95% CI, 0.27-0.45], *P*<0.001) vs placebo[1]

Take action when you see advanced, progressive PNET or advanced, progressive, well-differentiated, nonfunctional GI or lung NET

Well-established safety profile

- Adverse reactions were consistent with the known side effects of AFINITOR[6,7]
- There have been reports of noninfectious pneumonitis (including some with pulmonary hypertension as a secondary event), infections, and renal failure (including acute renal failure) in patients taking AFINITOR, some with fatal outcomes[1]
- GI and lung NET: The most common grade 3/4 adverse reactions (incidence ≥5%) were infections† (11%), diarrhea (9%), stomatitis‡ (9%), hyperglycemia (5%), and fatigue (5%)[1]
- PNET: The most common grade 3/4 adverse reactions (incidence ≥5%) were stomatitis§ (7%) and diarrhea‖ (5.5%)[1]

Trial designs

- PNET: RADIANT-3 was a randomized, double-blind, placebo-controlled, multicenter, phase 3 trial evaluating the efficacy and safety of AFINITOR + BSC (n=207) vs placebo + BSC (n=203) in patients with advanced, progressive PNET[1,7¶]
- GI and lung NET: RADIANT-4 was a randomized, double-blind, placebo-controlled, international, multicenter, phase 3 trial evaluating the efficacy and safety of AFINITOR + BSC (n=205) vs placebo + BSC (N=97) in patients with unresectable, locally advanced, or metastatic well-differentiated, nonfunctional GI (excluding pancreatic) or lung NET[1,6#]

Visit www.MoreAbout-AFINITOR.com to learn about the clinical results of AFINITOR.

Abbreviations: BSC, best supportive care; GI, gastrointestinal; NET, neuroendocrine tumors; PFS, progression-free survival; PNET, pancreatic neuroendocrine tumors; SSA, somatostatin analogue.

*See full Indications on front cover.

†Urinary tract infection, nasopharyngitis, upper respiratory tract infection, lower respiratory tract infection (pneumonia, bronchitis), abscess, pyelonephritis, septic shock, and viral myocarditis.

‡Includes stomatitis, mouth ulceration, aphthous stomatitis, gingival pain, glossitis, tongue ulceration, and mucosal inflammation.

§Includes stomatitis, aphthous stomatitis, gingival pain/swelling/ulceration, glossitis, glossodynia, lip ulceration, mouth ulceration, tongue ulceration, and mucosal inflammation.

‖Includes diarrhea, enteritis, enterocolitis, colitis, defecation urgency, and steatorrhea.

¶Eligibility criteria included advanced (unresectable or metastatic) pancreatic NET and evidence of disease progression ≤12 months prior to randomization. BSC could include SSA therapy.

#Eligibility criteria included well-differentiated (low- or intermediate-grade histology), no prior or current history of carcinoid symptoms, and evidence of disease progression ≤6 months prior to randomization. BSC included treatment deemed necessary by physician (eg, analgesics and antidiarrheals) except antitumor agents. Radiation or surgery were allowed only for palliative intent.

IMPORTANT SAFETY INFORMATION (continued)

Laboratory Abnormalities in Advanced, Progressive, Well-Differentiated, Nonfunctional GI and Lung NET: The most common laboratory abnormalities (incidence ≥50%, all grades) were anemia (81%), hypercholesterolemia (71%), lymphopenia (66%), elevated aspartate transaminase (57%), and hyperglycemia (55%). The most common grade 3/4 laboratory abnormalities (incidence ≥5%) were lymphopenia (17%), hyperglycemia (6%), elevated alanine transaminase (6%), hypokalemia (6%), and anemia (5%).

Please see additional Important Safety Information throughout.
Please see accompanying full Prescribing Information.

NOVARTIS

AFINITOR® (everolimus) tablets
2.5mg | 5mg | 7.5mg | 10mg

QR CODE FOR INTERNAL USE ONLY.

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

Printed in USA 10/17 AGN-1175903