HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AFINITOR safely and effectively. See full prescribing information for AFINITOR.

AFINITOR (everolimus) tablets for oral administration
Initial U.S. Approval: 2009

----------RECENT MAJOR CHANGES----------

Indications and Usage, Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer (1.1), Dosage and Administration (2.1, 2.2), Warnings and Precautions (5.1, 5.3, 5.5, 5.10) 07/2012
Indications and Usage (1.4, 1.5), Dosage and Administration (2.1, 2.2), Warnings and Precautions (5.1, 5.3, 5.8) 04/2012
Dosage and Administration (2.2, 2.4), Warnings and Precautions (5.7, 5.8) 03/2012

----------INDICATIONS AND USAGE----------

AFINITOR is a kinase inhibitor 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. (1.1)
- adults with progressive neuroendocrine tumors of pancreatic origin (PNET) that is unresectable, locally advanced or metastatic. The safety and effectiveness of AFINITOR in the treatment of patients with carcinoid tumors have not been established. (1.2)
- adults with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib. (1.3)
- adults with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery. The effectiveness of AFINITOR in treatment of renal angiomyolipoma is based on an analysis of durable objective responses in patients treated for a median of 8.3 months. Further follow-up of patients is required to determine long-term outcomes. (1.4)
- adults and children ≥ 3 years of age with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TSC) who require therapeutic intervention but are not candidates for curative surgical resection. The effectiveness of AFINITOR is based on an analysis of change in SEGA volume. Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated. (1.5)

----------DOSAGE AND ADMINISTRATION----------

Advanced HR+ BC, advanced PNET, advanced RCC, or renal angiomyolipoma with TSC:

- 10 mg once daily with or without food. (2.1)
- For patients with hepatic impairment, reduce the AFINITOR dose. (2.2)
- If moderate inhibitors of CYP3A4 and/or P-glycoprotein (PgP) are required, reduce the AFINITOR dose to 2.5 mg once daily; if tolerated, consider increasing to 5 mg once daily. (2.2)
- If strong inducers of CYP3A4 are required, increase AFINITOR dose in 5 mg increments to a maximum of 20 mg once daily. (2.2)

SEGA:

- Initial dose based on body surface area with subsequent titration to attain trough concentrations of 5-10 ng/mL. (2.3)
- If moderate inhibitors of CYP3A4 and/or PgP are required, reduce the AFINITOR dose by approximately 50%. Subsequent dosing should be based on therapeutic drug monitoring (TDM). (2.4)
- If strong inducers of CYP3A4 are required, double the AFINITOR dose. Subsequent dosing should be based on TDM. (2.4)

Dose reduction or treatment interruption may be needed to manage adverse drug reactions. (2.2, 2.4)

----------DOSAGE FORMS AND STRENGTHS----------

2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets with no score (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to everolimus, to other rapamycin derivatives, or to any of the excipients (4)

----------WARNINGS AND PRECAUTIONS----------

- Non-infectious pneumonitis: Monitor for clinical symptoms or radiological changes; fatal cases have occurred. Manage by dose reduction or discontinuation until symptoms resolve, and consider use of corticosteroids. (5.1)
- Infections: Increased risk of infections, some fatal. Monitor for signs and symptoms, and treat promptly. (5.2)
- Oral ulceration: Mouth ulcers, stomatitis, and oral mucositis are common. Management includes mouthwashes (without alcohol or peroxide) and topical treatments. (5.3)
- Renal failure: Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with AFINITOR. (5.4)
- Laboratory test alterations: Elevations of serum creatinine, blood glucose, and lipids may occur. Decreases in hemoglobin, neutrophils, and platelets may also occur. Monitor renal function, blood glucose, lipids, and hematologic parameters prior to treatment and periodically thereafter. (5.6)
- Vaccinations: Avoid live vaccines and close contact with those who have received live vaccines. (5.9)
- Embryo-fetal toxicity: Fetal harm can occur when administered to a pregnant woman. Apprise women of potential harm to the fetus. (5.10, 8.1)

----------ADVERSE REACTIONS----------

Advanced HR+ BC, Advanced PNET, Advanced RCC: Most common adverse reactions (incidence ≥30%) include stomatitis, infections, rash, fatigue, diarrhea, edema, abdominal pain, nausea, fever, asthenia, cough, headache and decreased appetite. (6.1, 6.2, 6.3)
Renal angiomyolipoma with TSC: Most common adverse reaction (incidence ≥ 30%) is stomatitis. (6.4)
SEGA: Most common adverse reactions (incidence ≥ 30%) are stomatitis, upper respiratory tract infection, sinusitis, otitis media, and pyrexia. (6.5)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong CYP3A4 inhibitors: Avoid concomitant use. (2.2, 2.4, 5.7, 7.1)
- Moderate CYP3A4 and/or PgP inhibitors: If combination is required, use caution and reduce dose of AFINITOR. (2.2, 2.4, 5.7, 7.1)
- Strong CYP3A4 inducers: Avoid concomitant use. If combination cannot be avoided, increase dose of AFINITOR. (2,2, 2.4, 5.7, 7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing mothers: Discontinue drug or nursing, taking into consideration the importance of drug to the mother. (8.3)
- Hepatic impairment: For advanced HR+ BC, advanced PNET, advanced RCC, and renal angiomyolipoma with TSC patients with hepatic impairment, reduce AFINITOR dose. For SEGA patients with Child-Pugh class A or Child-Pugh class B hepatic impairment, adjustment to the starting dose may not be needed; however, subsequent dosing should be based on TDM. AFINITOR should not be used in SEGA patients with Child-Pugh class C hepatic impairment. (2.2, 2.4, 5.8, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 07/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer (Advanced HR+ BC)

AFINITOR® 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.

1.2 Advanced Neuroendocrine Tumors of Pancreatic Origin (PNET)

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

The safety and effectiveness of AFINITOR® in the treatment of patients with carcinoid tumors have not been established.

1.3 Advanced Renal Cell Carcinoma (RCC)

AFINITOR® is indicated for the treatment of adult patients with advanced RCC after failure of treatment with sunitinib or sorafenib.

1.4 Renal Angiomyolipoma with Tuberous Sclerosis Complex (TSC)

AFINITOR® is indicated for the treatment of adult patients with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery.

The effectiveness of AFINITOR in treatment of renal angiomyolipoma is based on an analysis of durable objective responses in patients treated for a median of 8.3 months. Further follow-up of patients is required to determine long-term outcomes.

1.5 Subependymal Giant Cell Astrocytoma (SEGA)

AFINITOR® is indicated for the treatment of adult and pediatric patients, 3 years of age or older, with SEGA associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not candidates for curative surgical resection.

The effectiveness of AFINITOR is based on an analysis of change in SEGA volume *[see Clinical Studies (14.5)]*. Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated.

2 DOSAGE AND ADMINISTRATION

AFINITOR should be administered orally once daily at the same time every day, either consistently with food or consistently without food *[see Clinical Pharmacology (12.3)]*.

AFINITOR tablets should be swallowed whole with a glass of water. AFINITOR tablets should not be crushed. Do not take tablets which are crushed or broken. For patients unable to swallow tablets, AFINITOR tablet(s) should be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring, immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse should be completely swallowed to ensure that the entire dose is administered.

Continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs.

2.1 Recommended Dose in Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer, Advanced PNET, Advanced RCC and Renal Angiomyolipoma with TSC

The recommended dose of AFINITOR is 10 mg, to be taken once daily.

2.2 Dose Modifications in Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer, Advanced PNET, Advanced RCC, and Renal Angiomyolipoma with TSC

Management of Adverse Reactions

Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption of AFINITOR therapy. If dose reduction is required, the suggested dose is approximately 50% lower than the daily dose previously administered *[see Warnings and Precautions (5)]*.

Table 1 summarizes recommendations for dose reduction, interruption or discontinuation of AFINITOR in the management of adverse reactions. General management recommendations are also provided as applicable. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk

Table 1: AFINITOR Dose Adjustment and Management Recommendation for Adverse Reactions

Adverse Drug Reaction	Severity[a]	AFINITOR Dose Adjustment[b] and Management Recommendations
Non-infectious pneumonitis	Grade 1 Asymptomatic, radiographic findings only	No dose adjustment required. Initiate appropriate monitoring.
	Grade 2 Symptomatic, not interfering with ADL[c]	Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to ≤ grade 1. Re-initiate AFINITOR at a lower dose. Discontinue treatment if failure to recover within 4 wks.
	Grade 3 Symptomatic, interfering with ADL[c]; O_2 indicated	Interrupt AFINITOR until symptoms resolve to ≤ grade 1. Rule out infection, and consider treatment with corticosteroids. Consider re-initiating AFINITOR at a lower dose. If toxicity recurs at grade 3, consider discontinuation.
	Grade 4 Life-threatening, ventilatory support indicated	Discontinue AFINITOR, rule out infection, and consider treatment with corticosteroids.
Stomatitis	Grade 1 Minimal symptoms, normal diet	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouth wash several times a day.
	Grade 2 Symptomatic but can eat and swallow modified diet	Temporary dose interruption until recovery to grade ≤1. Re-initiate AFINITOR at the same dose. If stomatitis recurs at grade 2, interrupt dose until recovery to grade ≤1. Re-initiate AFINITOR at a lower dose. Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]
	Grade 3 Symptomatic and unable to adequately aliment or hydrate orally	Temporary dose interruption until recovery to grade ≤1. Re-initiate AFINITOR at a lower dose. Manage with topical analgesic mouth treatments (i.e. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]
	Grade 4 Symptoms associated with life-threatening consequences	Discontinue AFINITOR and treat with appropriate medical therapy.
Other non-hematologic toxicities (excluding metabolic events)	Grade 1	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor. If toxicity becomes intolerable, temporary dose interruption until recovery to grade ≤1. Re-initiate AFINITOR at the same dose. If toxicity recurs at grade 2, interrupt AFINITOR until recovery to grade ≤1. Re-initiate AFINITOR at a lower dose.
	Grade 3	Temporary dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Consider re-initiating AFINITOR at a lower dose. If toxicity recurs at grade 3, consider discontinuation.
	Grade 4	Discontinue AFINITOR and treat with appropriate medical therapy.
Metabolic events (e.g. hyperglycemia, dyslipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.

Adverse Drug Reaction	Severity[a]	AFINITOR Dose Adjustment[b] and Management Recommendations
	Grade 3	Temporary dose interruption. Re-initiate Afinitor at a lower dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue AFINITOR and treat with appropriate medical therapy.

[a] Severity grade description: 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms.

[b] If dose reduction is required, the suggested dose is approximately 50% lower than the dose previously administered.

[c] Activities of daily living (ADL)

[d] Avoid using agents containing hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

Hepatic Impairment

Hepatic impairment will increase the exposure to everolimus *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.7)]*. Dose adjustments are recommended:

- Mild hepatic impairment (Child-Pugh class A) – The recommended dose is 7.5 mg daily; the dose may be decreased to 5 mg if not well tolerated.

- Moderate hepatic impairment (Child-Pugh class B) – The recommended dose is 5 mg daily; the dose may be decreased to 2.5 mg if not well tolerated.

- Severe hepatic impairment (Child-Pugh class C) – If the desired benefit outweighs the risk, a dose of 2.5 mg daily may be used but must not be exceeded.

Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment.

CYP3A4 and/or P-glycoprotein (PgP) Inhibitors

Avoid the use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) *[see Warnings and Precautions (5.7) and Drug Interactions (7.1)]*.

Use caution when co-administered with moderate CYP3A4 and/or PgP inhibitors (e.g., amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem). If patients require co-administration of a moderate CYP3A4 and/or PgP inhibitor, reduce the AFINITOR dose to 2.5 mg daily. The reduced dose of AFINITOR is predicted to adjust the area under the curve (AUC) to the range observed without inhibitors. An AFINITOR dose increase from 2.5 mg to 5 mg may be considered based on patient tolerance. If the moderate inhibitor is discontinued, a washout period of approximately 2 to 3 days should be allowed before the AFINITOR dose is increased. If the moderate inhibitor is discontinued, the AFINITOR dose should be returned to the dose used prior to initiation of the moderate CYP3A4 and/or PgP inhibitor.

Strong CYP3A4 Inducers

Avoid the use of concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital). If patients require co-administration of a strong CYP3A4 inducer, consider increasing the AFINITOR dose from 10 mg daily up to 20 mg daily, using 5 mg increments. This dose of AFINITOR is predicted, based on pharmacokinetic data, to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued, the AFINITOR dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer *[see Warnings and Precautions (5.7) and Drug Interactions (7.2)]*.

Grapefruit, grapefruit juice, and other foods that are known to inhibit cytochrome P450 and PgP activity may increase everolimus exposures and should be avoided during treatment. St. John's Wort (*Hypericum perforatum*) may decrease everolimus exposure unpredictably and should be avoided.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.