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----------

Dosage and Administration (2.2, 2.4), Warnings and Precautions: Drug-drug Interactions (5.6), Hepatic Impairment (5.7) 03/2012
Indications and Usage, Advanced Pancreatic Neuroendocrine Tumors (1.1), Warnings and Precautions: Non-infectious Pneumonitis (5.1), Infections (5.2), Oral Ulceration (5.3), Renal Failure Events (5.4), Laboratory Tests and Monitoring (5.5) 05/2011

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

AFINITOR is a kinase inhibitor indicated for the treatment of patients 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. (1.1)
- advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib. (1.2)
- subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) 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. (1.3)

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

Advanced PNET or advanced RCC:

- 10 mg once daily with or without food. (2.1)
- For patients with hepatic impairment, reduce the AFINITOR dose. (2.2, 2.4)
- 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 and/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 events: 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. (5.5)
- Vaccinations: Avoid live vaccines and close contact with those who have received live vaccines. (5.8)
- Use in pregnancy: Fetal harm can occur when administered to a pregnant woman. Apprise women of potential harm to the fetus. (5.9, 8.1)

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

Advanced PNET: Most common adverse reactions (incidence ≥30%) are stomatitis, rash, diarrhea, fatigue, edema, abdominal pain, nausea, fever, and headache. (6.1)
Advanced RCC: Most common adverse reactions (incidence ≥30%) are stomatitis, infections, asthenia, fatigue, cough, and diarrhea. (6.2)
SEGA: Most common adverse reactions (incidence ≥30%) are stomatitis, upper respiratory tract infection, sinusitis, otitis media, and pyrexia. (6.3)

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, 5.6, 7.1)
- Moderate CYP3A4 and/or PgP inhibitors: If combination is required, use caution and reduce dose of AFINITOR. (2.2, 2.4, 5.6, 7.1)
- Strong CYP3A4 inducers: Avoid concomitant use. If combination cannot be avoided, increase dose of AFINITOR. (2.2, 2.4, 5.6, 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 PNET and advanced RCC patients with hepatic impairment, reduce AFINITOR dose. For SEGA patients with Child-Pugh class A and 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, 2.5, 5.7, 8.7)

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

Revised: 03/2012

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 Neuroendocrine Tumors of Pancreatic Origin (PNET)

AFINITOR® is indicated for the treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) in patients 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.

1.2 Advanced Renal Cell Carcinoma (RCC)

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

1.3 Subependymal Giant Cell Astrocytoma (SEGA)

AFINITOR® is indicated for the treatment of patients with SEGA associated with tuberous sclerosis (TS) 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 (14.2)]*. 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. The tablets should not be chewed or crushed. 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 Pancreatic Neuroendocrine Tumors and Advanced Renal Cell Carcinoma

The recommended dose of AFINITOR for treatment of advanced PNET and advanced RCC is 10 mg, to be taken once daily.

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

2.2 Dose Modifications in Advanced Pancreatic Neuroendocrine Tumors and Advanced Renal Cell Carcinoma

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 5 mg daily *[see Warnings and Precautions (5.1)]*.

Hepatic Impairment

Hepatic impairment will increase the exposure to everolimus *[see Warnings and Precautions (5.7) 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 (5.6) 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

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 (based on pharmacokinetic data), using 5 mg increments. This dose of AFINITOR is predicted 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 (5.6) 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.

2.3 Recommended Dose in Subependymal Giant Cell Astrocytoma

The recommended starting dose of AFINITOR for treatment of patients with SEGA is according to Table 1:

Table 1: Recommended Starting Dose of AFINITOR for Treatment of Patients with SEGA

Body Surface Area (BSA)	Starting Dose
0.5 m^2 to 1.2 m^2	2.5 mg once daily
1.3 m^2 to 2.1 m^2	5 mg once daily
Greater than or equal to 2.2 m^2	7.5 mg once daily

Patients receiving AFINITOR may require dose adjustments based on everolimus whole blood trough concentrations achieved, tolerability, individual response, and change in concomitant medications including CYP3A4-inducing antiepileptic drugs *[see Warnings and Precautions (5.6) and Drug Interactions (7.1, 7.2)]*. Dose adjustments can be made at two week intervals *[see Dosage and Administration (2.4, 2.5)]*.

Evaluate SEGA volume approximately 3 months after commencing AFINITOR therapy and periodically thereafter, with subsequent dose adjustments taking into consideration changes in SEGA volume, corresponding trough concentration, and tolerability. Responses have been observed at trough concentrations as low as 3 ng/mL; as such, once acceptable efficacy has been achieved, additional dose increases may not be necessary.

AFINITOR has not been studied in patients with SEGA < 3 years of age or with BSA < 0.58 m^2.

The optimal duration of therapy for patients with SEGA is unknown.

2.4 Dose Modifications in Subependymal Giant Cell Astrocytoma

Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption of AFINITOR therapy *[see Warnings and Precautions (5.1)]*. If dose reduction is required for patients receiving 2.5 mg daily, consider alternate day dosing.

Hepatic Impairment

Adjustment to the recommended starting dose for patients with SEGA who have mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment may not be needed; however, subsequent dosing should be based on therapeutic drug monitoring (TDM).

AFINITOR is not recommended for use in patients with SEGA who have severe hepatic impairment (Child-Pugh class C).

Everolimus whole blood trough concentration should be assessed approximately 2 weeks after commencing treatment or after any change in hepatic status (Child-Pugh). Dosing should be titrated to attain trough concentrations of 5 to 10 ng/mL *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

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 (5.5) 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 by approximately 50% to maintain trough concentrations of 5 to 10 ng/mL. If dose reduction is required for patients receiving 2.5 mg daily, consider alternate day dosing. Subsequent dosing should be individualized based on therapeutic drug monitoring. Everolimus trough concentrations should be assessed approximately 2 weeks after the addition of a moderate CYP3A4 and/or PgP inhibitor. 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 and the everolimus trough concentration should be re-assessed approximately 2 weeks later *[see Dosage and Administration (2.5), Warnings and Precautions (5.6) and Drug Interactions (7.1)]*.

Strong CYP3A4 Inducers

Avoid the use of concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital). For patients requiring a concomitant strong CYP3A4 inducer, double the AFINITOR dose. Subsequent dosing should be individualized based on therapeutic drug monitoring. If the strong inducer is discontinued, the AFINITOR dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer and the everolimus trough concentrations should be assessed approximately 2 weeks later *[see Dosage and Administration (2.5), Warnings and Precautions (5.6) 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.

2.5 Therapeutic Drug Monitoring in Subependymal Giant Cell Astrocytoma

Routine everolimus whole blood therapeutic drug concentration monitoring is recommended for all patients using a validated assay. Trough concentrations should be assessed approximately 2 weeks after commencing treatment. Dosing should be titrated to attain trough concentrations of 5 to 10 ng/mL.

There is limited safety experience with patients having trough concentrations > 10 ng/mL. If concentrations are between 10 to 15 ng/mL, and the patient has demonstrated adequate tolerability and tumor response, no dose reductions are needed. The dose of AFINITOR should be reduced if trough concentrations > 15 ng/mL are observed.

If concentrations are < 5 ng/mL, the daily dose may be increased by 2.5 mg every 2 weeks, subject to tolerability. Daily dose may be reduced by 2.5 mg every 2 weeks to attain a target of 5 to 10 ng/mL. If dose reduction is required for patients receiving 2.5 mg daily, alternate day dosing should be used.

Trough concentrations should be assessed approximately 2 weeks after any change in dose, after an initiation or change in co-administration of CYP3A4 and/or PgP inducers or inhibitors, or after any change in hepatic status (Child-Pugh Classification) *[see Dosage and Administration (2.4), Warnings and Precautions (5.6), Drug Interactions (7.1, 7.2)]*.

3 DOSAGE FORMS AND STRENGTHS

2.5 mg tablet
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with "LCL" on one side and "NVR" on the other.

5 mg tablet
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with "5" on one side and "NVR" on the other.

7.5 mg tablet
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with "7P5" on one side and "NVR" on the other.

10 mg tablet
White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with "UHE" on one side and "NVR" on the other.

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