

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, Renal Angiomyolipoma with Tuberous Sclerosis Complex (1.3), Subependymal Giant Cell Astrocytoma (1.4), Dosage and Administration (2.1, 2.2), Warnings and Precautions (5.1, 5.3, 5.7) 04/2012
Dosage and Administration (2.2, 2.4), Warnings and Precautions (5.6, 5.7) 03/2012
Indications and Usage, Advanced Pancreatic Neuroendocrine Tumors (1.1), Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5) 05/2011

INDICATIONS AND USAGE

AFINITOR is a kinase inhibitor indicated for the treatment of:

- 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. (1.1)
- adults with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib. (1.2)
- 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. (1.3)
- 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. (1.4)

DOSAGE AND ADMINISTRATION

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. (5.5)
- 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 $\geq 30\%$) are stomatitis, rash, diarrhea, fatigue, edema, abdominal pain, nausea, fever, and headache. (6.1)

Advanced RCC: Most common adverse reactions (incidence $\geq 30\%$) are stomatitis, infections, asthenia, fatigue, cough, and diarrhea. (6.2)

Renal angiomyolipoma with TSC: Most common adverse reaction (incidence $\geq 30\%$) is stomatitis. (6.3)

SEGA: Most common adverse reactions (incidence $\geq 30\%$) are stomatitis, upper respiratory tract infection, sinusitis, otitis media, and pyrexia. (6.4)

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, 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, 5.7, 8.7)

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

Revised: 04/2012

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 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.

1.2 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.

1.3 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.

1.4 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 (14.4)*]. 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. 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 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 PNET, Advanced RCC, and Renal Angiomyolipoma with TSC

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 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 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 (5.6) 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:

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 m².

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

2.4 Dose Modifications in Subependymal Giant Cell Astrocytoma

Adverse Reactions

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 (5.6) 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 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 and 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, 5.7), 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.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients. Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain, or angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus and other rapamycin derivatives.

5 WARNINGS AND PRECAUTIONS

5.1 Non-infectious Pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including AFINITOR. Non-infectious pneumonitis was reported in up to 14% of patients treated with AFINITOR in clinical trials. The incidence of Common Terminology Criteria (CTC) Grade 3 and 4 non-infectious pneumonitis was up to 4.0% and up to 0.1%, respectively [see *Adverse Reactions* (6.1, 6.2, 6.3, 6.4)]. Fatal outcomes have been observed.

Consider a diagnosis of non-infectious pneumonitis in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, or dyspnea, and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations. Advise patients to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue AFINITOR therapy without dose alteration. Imaging appears to overestimate the incidence of clinical pneumonitis.

If symptoms are moderate, consider interrupting therapy until symptoms improve. The use of corticosteroids may be indicated. AFINITOR may be reintroduced at a daily dose approximately 50% lower than the dose previously administered.

For cases where symptoms of non-infectious pneumonitis are severe, discontinue AFINITOR therapy. Corticosteroids may be indicated until clinical symptoms resolve. AFINITOR may be re-initiated at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances. The development of pneumonitis has been reported even at a reduced dose.

5.2 Infections

AFINITOR has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoal infections, including infections with opportunistic pathogens [see *Adverse Reactions* (6.1, 6.2, 6.3, 6.4)]. Localized and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis, and viral infections including reactivation of hepatitis B virus have occurred in patients taking AFINITOR. Some of these infections have been severe (e.g., leading to respiratory or hepatic failure) or fatal. Physicians and patients should be aware of the increased risk of infection with AFINITOR. Complete treatment of pre-existing invasive fungal infections prior to starting treatment with AFINITOR. While taking AFINITOR, be vigilant for signs and symptoms of infection; if a diagnosis of an infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of AFINITOR. If a diagnosis of invasive systemic fungal infection is made, discontinue AFINITOR and treat with appropriate antifungal therapy.

5.3 Oral Ulceration

Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with AFINITOR at an incidence ranging from 44-86% across the clinical trial experience. Grade 3 or 4 stomatitis was reported in 4-7% of patients [see *Adverse Reactions* (6.1, 6.2, 6.3, 6.4)]. In such cases, topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed [see *Drug Interactions* (7.1)].

5.4 Renal Failure

Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with AFINITOR [see *Laboratory Tests and Monitoring* (5.5)].

5.5 Laboratory Tests and Monitoring

Renal Function

Elevations of serum creatinine and proteinuria have been reported in clinical trials [see *Adverse Reactions (6.1, 6.2, 6.3, 6.4)*]. Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein, or serum creatinine, is recommended prior to the start of AFINITOR therapy and periodically thereafter.

Blood Glucose and Lipids

Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported in clinical trials [see *Adverse Reactions (6.1, 6.2, 6.3, 6.4)*]. Monitoring of fasting serum glucose and lipid profile is recommended prior to the start of AFINITOR therapy and periodically thereafter. When possible, optimal glucose and lipid control should be achieved before starting a patient on AFINITOR.

Hematologic Parameters

Decreased hemoglobin, lymphocytes, neutrophils, and platelets have been reported in clinical trials [see *Adverse Reactions (6.1, 6.2, 6.3, 6.4)*]. Monitoring of complete blood count is recommended prior to the start of AFINITOR therapy and periodically thereafter.

5.6 Drug-drug Interactions

Due to significant increases in exposure of everolimus, co-administration with strong CYP3A4 inhibitors should be avoided [see *Dosage and Administration (2.2, 2.4)* and *Drug Interactions (7.1)*].

A reduction of the AFINITOR dose is recommended when co-administered with a moderate CYP3A4 and/or Pgp inhibitor [see *Dosage and Administration (2.2, 2.4)* and *Drug Interactions (7.1)*].

An increase in the AFINITOR dose is recommended when co-administered with a strong CYP3A4 inducer [see *Dosage and Administration (2.2, 2.4)* and *Drug Interactions (7.2)*].

5.7 Hepatic Impairment

Exposure to everolimus was increased in patients with hepatic impairment [see *Clinical Pharmacology (12.3)*].

For advanced PNET, advanced RCC, and renal angiomyolipoma with TSC 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 [see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)*].

For SEGA patients with severe hepatic impairment, AFINITOR is not recommended. For SEGA patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, adjustment to the starting dose may not be needed; however subsequent dosing should be individualized based on therapeutic drug monitoring [see *Dosage and Administration (2.4, 2.5)*].

5.8 Vaccinations

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with AFINITOR. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

The timing of routine vaccinations in pediatric patients with SEGA should be considered prior to the start of everolimus therapy.

5.9 Use in Pregnancy

There are no adequate and well-controlled studies of AFINITOR in pregnant women. However, based on the mechanism of action, AFINITOR may cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use an effective method of contraception while using AFINITOR and for up to 8 weeks after ending treatment [see *Use in Specific Populations (8.1)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label [see *Warnings and Precautions (5)*]:

- Non-infectious pneumonitis [see Warnings and Precautions (5.1)].
- Infections [see Warnings and Precautions (5.2)].
- Oral ulcers [see Warnings and Precautions (5.3)].
- Renal failure [see Warnings and Precautions (5.4)].

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

6.1 Clinical Study Experience in Advanced Pancreatic Neuroendocrine Tumors

In a randomized, controlled trial of AFINITOR (n=204) versus placebo (n=203) in patients with advanced PNET the median age of patients was 58 years (range 20-87), 79% were Caucasian, and 55% were male. Patients on the placebo arm could cross over to open-label AFINITOR upon disease progression.

The most common adverse reactions (incidence $\geq 30\%$) were stomatitis, rash, diarrhea, fatigue, edema, abdominal pain, nausea, fever, and headache. The most common Grade 3-4 adverse reactions (incidence $\geq 5\%$) were stomatitis and diarrhea. The most common laboratory abnormalities (incidence $\geq 50\%$) were decreased hemoglobin, hyperglycemia, alkaline phosphatase increased, hypercholesterolemia, bicarbonate decreased, and increased aspartate transaminase (AST). The most common Grade 3-4 laboratory abnormalities (incidence $\geq 3\%$) were hyperglycemia, lymphopenia, decreased hemoglobin, hypophosphatemia, increased alkaline phosphatase, neutropenia, increased aspartate transaminase (AST), potassium decreased, and thrombocytopenia. Deaths during double-blind treatment where an adverse event was the primary cause occurred in 7 patients on AFINITOR and 1 patient on placebo. Causes of death on the AFINITOR arm included one case of each of the following: acute renal failure, acute respiratory distress, cardiac arrest, death (cause unknown), hepatic failure, pneumonia, and sepsis. There was 1 death due to pulmonary embolism on the placebo arm. After cross-over to open-label AFINITOR, there were 3 additional deaths, one due to hypoglycemia and cardiac arrest in a patient with insulinoma, one due to MI with CHF, and the other due to sudden death. The rates of treatment-emergent adverse events resulting in permanent discontinuation were 20% and 6% for the AFINITOR and placebo treatment groups, respectively. Dose delay or reduction was necessary in 61% of everolimus patients and 29% of placebo patients. Grade 3-4 renal failure occurred in 6 patients in the everolimus arm and 3 patients in the placebo arm. Thrombotic events included 5 patients with pulmonary embolus in the everolimus arm and 1 in the placebo arm as well as 3 patients with thrombosis in the everolimus arm and 2 in the placebo arm.

Table 2 compares the incidence of treatment-emergent adverse reactions reported with an incidence of $\geq 10\%$ for patients receiving AFINITOR 10 mg daily versus placebo.

Table 2: Adverse Reactions Reported $\geq 10\%$ of Patients with Advanced PNET

	AFINITOR N=204			Placebo N=203		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Any adverse reaction	100	49	13	98	32	8
Gastrointestinal disorders						
Stomatitis ^a	70	7	0	20	0	0
Diarrhea ^b	50	5	0.5	25	3	0
Abdominal pain	36	4	0	32	6	1
Nausea	32	2	0	33	2	0
Vomiting	29	1	0	21	2	0
Constipation	14	0	0	13	0.5	0
Dry mouth	11	0	0	4	0	0
General disorders and administration site conditions						
Fatigue/malaise	45	3	0.5	27	2	0.5
Edema (general and peripheral)	39	1	0.5	12	1	0
Fever	31	0.5	0.5	13	0.5	0
Asthenia	19	3	0	20	3	0
Infections and infestations						
Nasopharyngitis/rhinitis/URI	25	0	0	13	0	0
Urinary tract infection	16	0	0	6	0.5	0
Investigations						

	AFINITOR N=204			Placebo N=203		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
Weight decreased	28	0.5	0	11	0	0
Metabolism and nutrition disorders						
Decreased appetite	30	1	0	18	1	0
Diabetes mellitus	10	2	0	0.5	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	15	1	0.5	7	0.5	0
Back pain	15	1	0	11	1	0
Pain in extremity	14	0.5	0	6	1	0
Muscle spasms	10	0	0	4	0	0
Nervous system disorders						
Headache/migraine	30	0.5	0	15	1	0
Dysgeusia	19	0	0	5	0	0
Dizziness	12	0.5	0	7	0	0
Psychiatric disorders						
Insomnia	14	0	0	8	0	0
Respiratory, thoracic and mediastinal disorders						
Cough/productive cough	25	0.5	0	13	0	0
Epistaxis	22	0	0	1	0	0
Dyspnea/dyspnea exertional	20	2	0.5	7	0.5	0
Pneumonitis ^c	17	3	0.5	0	0	0
Oropharyngeal pain	11	0	0	6	0	0
Skin and subcutaneous disorders						
Rash	59	0.5	0	19	0	0
Nail disorders	22	0.5	0	2	0	0
Pruritus/pruritus generalized	21	0	0	13	0	0
Dry skin/xeroderma	13	0	0	6	0	0
Vascular disorders						
Hypertension	13	1	0	6	1	0
Median duration of treatment (wks)		37			16	

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

^b Includes diarrhea, enteritis, enterocolitis, colitis, defecation urgency, and steatorrhea.

^c Includes pneumonitis, interstitial lung disease, pulmonary fibrosis and restrictive pulmonary disease.

Key observed laboratory abnormalities are presented in Table 3.

Table 3: Key Laboratory Abnormalities Reported in $\geq 10\%$ of Patients with Advanced PNET

Laboratory parameter	AFINITOR N=204		Placebo N=203	
	All grades	Grade 3-4	All grades	Grade 3-4
	%	%	%	%
Hematology				
Hemoglobin decreased	86	15	63	1
Lymphocytes decreased	45	16	22	4
Platelets decreased	45	3	11	0
WBC decreased	43	2	13	0
Neutrophils decreased	30	4	17	2
Clinical chemistry				
Alkaline phosphatase increased	74	8	66	8
Glucose (fasting) increased	75	17	53	6
Cholesterol increased	66	0.5	22	0
Bicarbonate decreased	56	0	40	0

Aspartate transaminase (AST) increased	56	4	41	4
Alanine transaminase (ALT) increased	48	2	35	2
Phosphate decreased	40	10	14	3
Triglycerides increased	39	0	10	0
Calcium decreased	37	0.5	12	0
Potassium decreased	23	4	5	0
Creatinine increased	19	2	14	0
Sodium decreased	16	1	16	1
Albumin decreased	13	1	8	0
Bilirubin increased	10	1	14	2
Potassium increased	7	0	10	0.5

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6.2 Clinical Study Experience in Advanced Renal Cell Carcinoma

The data described below reflect exposure to AFINITOR (n=274) and placebo (n=137) in a randomized, controlled trial in patients with metastatic renal cell carcinoma who received prior treatment with sunitinib and/or sorafenib. The median age of patients was 61 years (range 27-85), 88% were Caucasian, and 78% were male. The median duration of blinded study treatment was 141 days (range 19-451) for patients receiving AFINITOR and 60 days (range 21-295) for those receiving placebo.

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 on the AFINITOR arm but none on the placebo arm. The rates of treatment-emergent adverse events (irrespective of causality) resulting in permanent discontinuation were 14% and 3% for the AFINITOR and placebo treatment groups, respectively. The most common adverse reactions (irrespective of causality) leading to treatment discontinuation were pneumonitis and dyspnea. Infections, stomatitis, and pneumonitis were the most common reasons for treatment delay or dose reduction. The most common medical interventions required during AFINITOR treatment were for infections, anemia, and stomatitis.

Table 4 compares the incidence of treatment-emergent adverse reactions reported with an incidence of $\geq 10\%$ for patients receiving AFINITOR 10 mg daily versus placebo. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

Table 4: Adverse Reactions Reported in at least 10% of Patients with RCC and at a Higher Rate in the AFINITOR Arm than in the Placebo Arm

Any adverse reaction	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
	%	%	%	%	%	%
Any adverse reaction	97	52	13	93	23	5
Gastrointestinal disorders						
Stomatitis ^a	44	4	<1	8	0	0
Diarrhea	30	1	0	7	0	0
Nausea	26	1	0	19	0	0
Vomiting	20	2	0	12	0	0
Infections and infestations^b	37	7	3	18	1	0
General disorders and administration site conditions						
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Edema peripheral	25	<1	0	8	<1	0
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	30	<1	0	16	0	0
Dyspnea	24	6	1	15	3	0
Epistaxis	18	0	0	0	0	0

	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Pneumonitis ^c	14	4	0	0	0	0
Skin and subcutaneous tissue disorders						
Rash	29	1	0	7	0	0
Pruritus	14	<1	0	7	0	0
Dry skin	13	<1	0	5	0	0
Metabolism and nutrition disorders						
Anorexia	25	1	0	14	<1	0
Nervous system disorders						
Headache	19	<1	<1	9	<1	0
Dysgeusia	10	0	0	2	0	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	10	1	0	7	0	0
Median duration of treatment (d)		141			60	

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^a Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.

^b Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (6%), pneumonia (6%), urinary tract infection (5%), bronchitis (4%), and sinusitis (3%), and also including aspergillosis (<1%), candidiasis (<1%), and sepsis (<1%).

^c Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

Other notable adverse reactions occurring more frequently with AFINITOR than with placebo, but with an incidence of < 10% include:

Gastrointestinal disorders: Abdominal pain (9%), dry mouth (8%), hemorrhoids (5%), dysphagia (4%)

General disorders and administration site conditions: Weight decreased (9%), chest pain (5%), chills (4%), impaired wound healing (< 1%)

Respiratory, thoracic and mediastinal disorders: Pleural effusion (7%), pharyngolaryngeal pain (4%), rhinorrhea (3%)

Skin and subcutaneous tissue disorders: Hand-foot syndrome (reported as palmar-plantar erythrodysesthesia syndrome) (5%), nail disorder (5%), erythema (4%), onychoclasia (4%), skin lesion (4%), acneiform dermatitis (3%)

Metabolism and nutrition disorders: Exacerbation of pre-existing diabetes mellitus (2%), new onset of diabetes mellitus (< 1%)

Psychiatric disorders: Insomnia (9%)

Nervous system disorders: Dizziness (7%), paresthesia (5%)

Eye disorders: Eyelid edema (4%), conjunctivitis (2%)

Vascular disorders: Hypertension (4%), deep vein thrombosis (< 1%)

Renal and urinary disorders: Renal failure (3%)

Cardiac disorders: Tachycardia (3%), congestive cardiac failure (1%)

Musculoskeletal and connective tissue disorders: Jaw pain (3%)

Hematologic disorders: Hemorrhage (3%)

Key laboratory abnormalities are presented in Table 5.

Table 5: Key Laboratory Abnormalities Reported in Patients with RCC at a Higher Rate in the AFINITOR Arm than the Placebo Arm

Laboratory parameter	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology^a						
Hemoglobin decreased	92	12	1	79	5	<1
Lymphocytes decreased	51	16	2	28	5	0
Platelets decreased	23	1	0	2	0	<1
Neutrophils decreased	14	0	<1	4	0	0
Clinical chemistry						

Cholesterol increased	77	4	0	35	0	0
Triglycerides increased	73	<1	0	34	0	0
Glucose increased	57	15	<1	25	1	0
Creatinine increased	50	1	0	34	0	0
Phosphate decreased	37	6	0	8	0	0
Aspartate transaminase (AST) increased	25	<1	<1	7	0	0
Alanine transaminase (ALT) increased	21	1	0	4	0	0
Bilirubin increased	3	<1	<1	2	0	0

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^a Includes reports of anemia, leukopenia, lymphopenia, neutropenia, pancytopenia, thrombocytopenia.

6.3 Clinical Study Experience in Renal Angiomyolipoma with Tuberous Sclerosis Complex

The data described below are based on a randomized (2:1), double-blind, placebo-controlled trial of AFINITOR in 118 patients with renal angiomyolipoma as a feature of TSC (n=113) or sporadic lymphangiomyomatosis (n=5). The median age of patients was 31 years (range 18 to 61 years), 89% were Caucasian, and 34% were male. The median duration of blinded study treatment was 48 weeks (range 2 to 115 weeks) for patients receiving AFINITOR and 45 weeks (range 9 to 115 weeks) for those receiving placebo.

The most common adverse reaction reported for AFINITOR (incidence $\geq 30\%$) was stomatitis. The most common Grade 3-4 adverse reactions (incidence $\geq 2\%$) were stomatitis, amenorrhea, and convulsion. The most common laboratory abnormalities (incidence $\geq 50\%$) were hypercholesterolemia, hypertriglyceridemia, and anemia. The most common Grade 3-4 laboratory abnormality (incidence $\geq 3\%$) was hypophosphatemia.

The rate of treatment-emergent adverse events resulting in permanent discontinuation was 3.8% in the AFINITOR-treated patients. Adverse reactions leading to permanent discontinuation in the AFINITOR arm were hypersensitivity/angioedema/bronchospasm, convulsion, and hypophosphatemia. Dose adjustments (interruptions or reductions) due to adverse reactions occurred in 52% of AFINITOR-treated patients. The most common adverse reaction leading to AFINITOR dose adjustment was stomatitis.

Table 6 compares the incidence of treatment-emergent adverse reactions reported with an incidence of $\geq 10\%$ for patients receiving AFINITOR and occurring more frequently with AFINITOR than with placebo. Laboratory abnormalities are described separately in Table 7.

Table 6: Treatment-emergent Adverse Reactions Reported in $\geq 10\%$ of AFINITOR-treated Patients with Renal Angiomyolipoma

	AFINITOR N=79			Placebo N=39		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Any adverse reaction	100	25	5	97	8	5
Stomatitis ^a	78	6	0	23	0	0
Nausea	16	0	0	13	0	0
Vomiting	15	0	0	5	0	0
Diarrhea	14	0	0	5	0	0
Abdominal pain	11	0	0	8	3	0
Peripheral edema	13	0	0	8	0	0
Upper respiratory tract infection	11	0	0	5	0	0
Arthralgia	13	0	0	5	0	0
Headache	22	0	0	21	3	0
Cough	20	0	0	13	0	0
Acne	22	0	0	5	0	0
Eczema	10	0	0	8	0	0

Grading according to CTCAE Version 3.0

^a Includes stomatitis, aphthous stomatitis, mouth ulceration, gingival pain, glossitis, and glossodynia.

Amenorrhea occurred in 15% of AFINITOR-treated females (8 of 52) and 4% (1 of 26) of females in the placebo group. Other adverse reactions involving the female reproductive system were menorrhagia (10%), menstrual irregularities (10%), and vaginal hemorrhage (8%).

Other notable adverse reactions occurring more frequently with AFINITOR than with placebo, but with an incidence of < 10% include:

Immune system disorders: Hypersensitivity (3%)

Infections and infestations: Otitis media (6%), sinusitis (6%), pustular rash (5%)

Metabolism and nutrition disorders: Decreased appetite (6%)

Nervous system disorders: Convulsions (5%), migraine (5%), dysgeusia (4%), ageusia (1%)

Psychiatric disorders: Depression (5%)

Respiratory, thoracic and mediastinal disorders: Epistaxis (9%), pneumonitis (1%)

Skin and subcutaneous tissue disorders: Dry skin (9%), dermatitis acneiform (8%), papule (5%)

Vascular disorders: Hypertensive crisis (1%)

Table 7: Key Laboratory Abnormalities Reported in AFINITOR-treated Patients with Renal Angiomyolipoma

	AFINITOR N=79			Placebo N=39		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology						
Anemia	61	0	0	49	0	0
Leucopenia	37	0	0	21	0	0
Neutropenia	25	0	1	26	0	0
Lymphopenia	20	1	0	8	0	0
Thrombocytopenia	19	0	0	3	0	0
Hypercholesterolemia	85	1	0	46	0	0
Hypertriglyceridemia	52	0	0	10	0	0
Hypophosphatemia	49	5	0	15	0	0
Alkaline phosphatase increased	32	1	0	10	0	0
Elevated aspartate transaminase (AST)	23	1	0	8	0	0
Elevated alanine transaminase (ALT)	20	1	0	15	0	0
Fasting hyperglycemia	14	0	0	8	0	0

Grading according to CTCAE Version 3.0

6.4 Clinical Study Experience in Subependymal Giant Cell Astrocytoma

The data described below reflect exposure to AFINITOR (n=28) in an open-label, single-arm trial for the treatment of patients with SEGA. The reliability of the frequency of adverse reactions and laboratory abnormalities reported in this trial is limited because of the small number of patients. The median age of patients was 11 years (range 3-34), 86% were Caucasian, and 61% were male. In total, 17 of the 28 patients were exposed to AFINITOR for \geq 21 months.

The most common adverse reactions (incidence \geq 30%) were stomatitis, upper respiratory tract infection, sinusitis, otitis media, and pyrexia. The Grade 3 adverse reactions were convulsion, infections (single cases of sinusitis, pneumonia, tooth infection, and bronchitis viral), and single cases of stomatitis, aspiration, cyclic neutropenia, sleep apnea syndrome, vomiting, dizziness, white blood cell count decreased, and neutrophil count decreased. A Grade 4 convulsion was also reported.

Table 8 summarizes the incidence of treatment-emergent adverse reactions reported with an incidence of \geq 10%. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

Table 8: Adverse Reactions Reported in at least 10% of Patients with SEGA

	AFINITOR N=28	
	All grades %	Grade 4 %

Any adverse reaction	100	36	4
Gastrointestinal disorders			
Stomatitis	86	4	0
Diarrhea	25	0	0
Vomiting	21	4	0
Abdominal pain	11	0	0
Constipation	11	0	0
Infections and infestations			
Upper respiratory tract infection	82	0	0
Sinusitis	39	4	0
Otitis media	36	0	0
Cellulitis	21	0	0
Body tinea	18	0	0
Gastroenteritis	18	0	0
Skin infection	18	0	0
Gastric infection	14	0	0
Otitis externa	14	0	0
Pharyngitis	11	0	0
General disorders and administration site conditions			
Pyrexia	32	0	0
Nervous system disorders			
Convulsion	29	7	4
Headache	18	0	0
Dizziness	14	4	0
Skin and subcutaneous tissue disorders			
Dermatitis acneiform	25	0	0
Dry skin	18	0	0
Rash	18	0	0
Dermatitis contact	14	0	0
Acne	11	0	0
Respiratory, thoracic and mediastinal disorders			
Cough	21	0	0
Nasal congestion	14	0	0
Rhinitis allergic	14	0	0
Psychiatric disorders			
Personality change	18	0	0
Injury, poisoning and procedural complications			
Excoriation	14	0	0

CTCAE Version 3.0

Other notable adverse reactions occurring with an incidence of < 10% include:

Gastrointestinal disorders: Gastritis (7%)

Skin and subcutaneous tissue disorders: Pityriasis rosea (4%)

Investigations: Chest x-ray abnormal (4%)

General disorders and administration site conditions: Fatigue (7%), edema peripheral (4%)

Respiratory, thoracic and mediastinal disorders: Pharyngeal inflammation (7%)

Nervous system disorders: Somnolence (7%)

Psychiatric disorders: Anxiety (7%)

Renal and urinary disorders: Proteinuria (7%)

Eye disorders: Ocular hyperemia (4%)

Vascular disorders: Hypertension (4%)

Key Laboratory Abnormalities

Single cases of Grade 3 elevated aspartate transaminase (AST) concentrations and low absolute neutrophil count (ANC) were reported. No Grade 4 laboratory abnormalities were noted. Laboratory abnormalities observed in > 1 patient (and listed in decreasing order of frequency) included elevations in AST concentrations (89%), total cholesterol (68%), alanine transaminase (ALT) (46%), triglycerides (43%) (hypertriglyceridemia reported as adverse reaction in 11% of patients, blood triglycerides increased reported as adverse reaction in 7% of patients), glucose (25%), and creatinine (11%), and reductions in white blood cell counts (54%) (reported as adverse reaction in 11% of patients), hemoglobin (39%), glucose (32%), and platelet counts (21%). Most of these laboratory abnormalities were mild (Grade 1).

Two cases of neutrophil count decreased and blood immunoglobulin G decreased were reported as adverse reactions.

7 DRUG INTERACTIONS

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump PgP. *In vitro*, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

7.1 Agents that may Increase Everolimus Blood Concentrations

CYP3A4 Inhibitors and PgP Inhibitors

In healthy subjects, compared to AFINITOR treatment alone there were significant increases in everolimus exposure when AFINITOR was coadministered with:

- ketoconazole (a strong CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 3.9- and 15.0-fold, respectively.
- erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 2.0- and 4.4-fold, respectively.
- verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 2.3- and 3.5-fold, respectively.

Concomitant strong inhibitors of CYP3A4 should not be used [see *Dosage and Administration* (2.3, 2.5) and *Warnings and Precautions* (5.6)].

Use caution when AFINITOR is used in combination with moderate CYP3A4 and/or PgP inhibitors. If alternative treatment cannot be administered reduce the AFINITOR dose [see *Dosage and Administration* (2.3, 2.5) and *Warnings and Precautions* (5.6)].

7.2 Agents that may Decrease Everolimus Blood Concentrations

CYP3A4 Inducers

In healthy subjects, co-administration of AFINITOR with rifampin, a strong inducer of CYP3A4, decreased everolimus AUC and C_{max} by 63% and 58% respectively, compared to everolimus treatment alone. Consider a dose increase of AFINITOR when co-administered with strong CYP3A4 inducers if alternative treatment cannot be administered. St. John's Wort may decrease everolimus exposure unpredictably and should be avoided [see *Dosage and Administration* (2.3, 2.5)].

7.3 Agents whose Plasma Concentrations may be Altered by Everolimus

Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between AFINITOR and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of AFINITOR.

A study in healthy subjects demonstrated that co-administration of an oral dose of midazolam (sensitive CYP3A4 substrate) with everolimus resulted in a 25% increase in midazolam C_{max} and a 30% increase in midazolam AUC_(0-inf).

Coadministration of everolimus and depot octreotide increased octreotide C_{min} by approximately 50%.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [see *Warnings and Precautions* (5.9)].

There are no adequate and well-controlled studies of AFINITOR in pregnant women. However, based on the mechanism of action, AFINITOR may cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures. If this drug is used during pregnancy or

if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use an effective method of contraception while receiving AFINITOR and for up to 8 weeks after ending treatment.

In animal reproductive studies, oral administration of everolimus to female rats before mating and through organogenesis induced embryo-fetal toxicities, including increased resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, malformation (e.g., sternal cleft), and retarded skeletal development. These effects occurred in the absence of maternal toxicities. Embryo-fetal toxicities occurred at approximately 4% the exposure (AUC_{0-24h}) in patients receiving the 10 mg daily dose. In rabbits, embryotoxicity evident as an increase in resorptions occurred at an oral dose approximately 1.6 times the 10 mg daily human dose, and 0.7 times the maximum dose administered to SEGA patients on a body surface area basis. The effect in rabbits occurred in the presence of maternal toxicities.

In a pre- and post-natal development study in rats, animals were dosed from implantation through lactation. At approximately 10% of the 10 mg daily human dose, and 4% of the maximum dose administered to SEGA patients, based on body surface area, there were no adverse effects on delivery and lactation and there were no signs of maternal toxicity. However, there was reduced body weight (up to 9% reduction from the control) and slight reduction in survival in offspring (~5% died or missing). There were no drug-related effects on the developmental parameters (morphological development, motor activity, learning, or fertility assessment) in the offspring.

Doses that resulted in embryo-fetal toxicities in rats and rabbits were ≥ 0.1 mg/kg (0.6 mg/m²) and 0.8 mg/kg (9.6 mg/m²), respectively. The dose in the pre- and post-natal development study in rats that caused reduction in body weights and survival of offspring was 0.1 mg/kg (0.6 mg/m²).

8.3 Nursing Mothers

It is not known whether everolimus is excreted in human milk. Everolimus and/or its metabolites passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from everolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

AFINITOR is recommended for use only in patients with SEGA who are aged ≥ 3 years.

A prospective, open-label, single-arm trial was conducted to evaluate the safety and efficacy of AFINITOR in patients with SEGA associated with TSC. In total, 28 patients received treatment with AFINITOR; median age was 11 years (range 3-34). AFINITOR has not been studied in patients with SEGA < 3 years of age.

8.5 Geriatric Use

In the randomized advanced RCC study, 41% of AFINITOR-treated patients were ≥ 65 years of age, while 7% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out [see *Clinical Pharmacology* (12.3)].

No dosage adjustment is required in elderly patients [see *Clinical Pharmacology* (12.3)].

8.6 Renal Impairment

No clinical studies were conducted with AFINITOR in patients with decreased renal function. Renal impairment is not expected to influence drug exposure and no dosage adjustment of everolimus is recommended in patients with renal impairment [see *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

The safety, tolerability and pharmacokinetics of AFINITOR were evaluated in a 34 subject single oral dose study of everolimus in subjects with impaired hepatic function relative to subjects with normal hepatic function. Exposure was increased in patients with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment [see *Clinical Pharmacology* (12.3)].

For advanced PNET, advanced RCC, and renal angiomyolipoma with TSC patients with severe hepatic impairment, 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 [see *Dosage and Administration* (2.2)].

For SEGA patients with severe hepatic impairment (Child-Pugh class C), AFINITOR is not recommended. For SEGA patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, adjustment to the starting

dose may not be needed; however, subsequent dosing should be individualized based on therapeutic drug monitoring [see *Dosage and Administration* (2.4, 2.5)].

10 OVERDOSAGE

In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity were observed in either mice or rats given single oral doses of 2000 mg/kg (limit test).

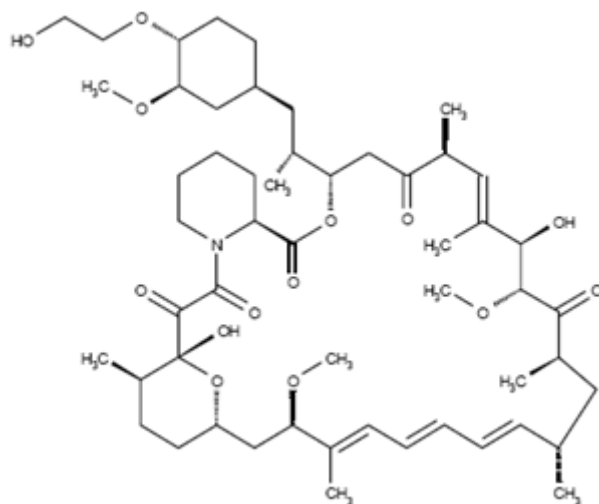
Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been administered. The acute toxicity profile observed with the 70 mg dose was consistent with that for the 10 mg dose.

11 DESCRIPTION

AFINITOR (everolimus), an inhibitor of mTOR, is an antineoplastic agent.

The chemical name of everolimus is (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-[(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxo-4-aza-tricyclo[30.3.1.0^{4,9}]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone.

The molecular formula is C₅₃H₈₃NO₁₄ and the molecular weight is 958.2. The structural formula is:



AFINITOR is supplied as tablets for oral administration containing 2.5 mg, 5 mg, 7.5 mg, or 10 mg of everolimus together with butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, and lactose anhydrous as inactive ingredients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Everolimus is an inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers. Everolimus binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation with mTORC1 and thus inhibition of mTOR kinase activity. Everolimus reduced the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP1), downstream effectors of mTOR, involved in protein synthesis. In addition, everolimus inhibited the expression of hypoxia-inducible factor (e.g., HIF-1) and reduced the expression of vascular endothelial growth factor (VEGF). Inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in *in vitro* and/or *in vivo* studies.

Two regulators of mTORC1 signaling are the oncogene suppressors tuberlin-sclerosis complexes 1 and 2 (*TSC1*, *TSC2*). Loss or inactivation of either *TSC1* or *TSC2* leads to activation of downstream signaling. In TSC, a genetic disorder, inactivating mutations in either the *TSC1* or the *TSC2* gene lead to hamartoma formation throughout the body.

12.2 Pharmacodynamics

QT/QTc Prolongation Potential

In a randomized, placebo-controlled, crossover study, 59 healthy subjects were administered a single oral dose of AFINITOR (20 mg and 50 mg) and placebo. There is no indication of a QT/QTc prolonging effect of AFINITOR in single doses up to 50 mg.

Exposure Response Relationships

Markers of protein synthesis show that inhibition of mTOR is complete after a 10 mg daily dose.

In patients with SEGA, higher everolimus trough concentrations appear to be associated with larger reductions in SEGA volume. However, as responses have been observed at trough concentrations as low as 3 ng/mL, once acceptable efficacy has been achieved, additional dose increase may not be necessary.

12.3 Pharmacokinetics

Absorption

In patients with advanced solid tumors, peak everolimus concentrations are reached 1 to 2 hours after administration of oral doses ranging from 5 mg to 70 mg. Following single doses, C_{max} is dose-proportional between 5 mg and 10 mg. At doses of 20 mg and higher, the increase in C_{max} is less than dose-proportional, however AUC shows dose-proportionality over the 5 mg to 70 mg dose range. Steady-state was achieved within 2 weeks following once-daily dosing.

Food effect: In healthy subjects, high fat meals reduced systemic exposure to AFINITOR 10 mg tablet (as measured by AUC) by 22% and the peak blood concentration C_{max} by 54%. Light fat meals reduced AUC by 32% and C_{max} by 42%. Food, however, had no apparent effect on the post absorption phase concentration-time profile.

Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given AFINITOR 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.

Metabolism

Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, everolimus is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus. These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100-times less activity than everolimus itself.

In vitro, everolimus competitively inhibited the metabolism of CYP3A4 and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan.

Excretion

No specific excretion studies have been undertaken in cancer patients. Following the administration of a 3 mg single dose of radiolabeled everolimus in patients who were receiving cyclosporine, 80% of the radioactivity was recovered from the feces, while 5% was excreted in the urine. The parent substance was not detected in urine or feces. The mean elimination half-life of everolimus is approximately 30 hours.

Patients with Renal Impairment

Approximately 5% of total radioactivity was excreted in the urine following a 3 mg dose of [14 C]-labeled everolimus. In a population pharmacokinetic analysis which included 170 patients with advanced cancer, no significant influence of creatinine clearance (25–178 mL/min) was detected on oral clearance (CL/F) of everolimus [*see Use in Specific Populations (8.6)*].

Patients with Hepatic Impairment

The safety, tolerability and pharmacokinetics of AFINITOR were evaluated in a single oral dose study of everolimus in subjects with impaired hepatic function relative to subjects with normal hepatic function. Compared to normal subjects (N=13), there was a 1.8-fold, 3.2-fold, and 3.6-fold increase in exposure (i.e. AUC) for subjects with mild (Child-Pugh class A, N=6), moderate (Child-Pugh class B, N=9), and severe (Child-Pugh class C, N=6) hepatic impairment, respectively. In another study, the average AUC of everolimus in eight subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in eight subjects with normal hepatic function.

For advanced PNET, advanced RCC, and renal angiomyolipoma with TSC patients with severe hepatic impairment, AFINITOR may be used at a reduced dose if the desired benefit outweighs the risk. For patients with moderate or mild hepatic impairment, a dose reduction is recommended [*see Dosage and Administration (2.2)*].

For SEGA patients with mild (Child-Pugh class A) or moderate hepatic impairment (Child-Pugh class B), adjustment to the starting dose may not be needed; however, subsequent dosing should be individualized based on therapeutic drug monitoring [see *Dosage and Administration* (2.4, 2.5)]. For SEGA patients with severe hepatic impairment (Child-Pugh class C), AFINITOR should not be used.

Effects of Age and Gender

In a population pharmacokinetic evaluation in cancer patients, no relationship was apparent between oral clearance and patient age or gender.

Ethnicity

Based on a cross-study comparison, Japanese patients (n=6) had on average exposures that were higher than non-Japanese patients receiving the same dose.

Based on analysis of population pharmacokinetics, oral clearance (CL/F) is on average 20% higher in Black patients than in Caucasians.

The significance of these differences on the safety and efficacy of everolimus in Japanese or Black patients has not been established.

Dose Proportionality in Patients with SEGA

In patients with SEGA, intra-patient steady-state trough concentrations were dose-proportional at daily doses of 1.5 to 14.6 mg/m² [see *Dosage and Administration* (2.3, 2.4)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Administration of everolimus for up to 2 years did not indicate oncogenic potential in mice and rats up to the highest doses tested (0.9 mg/kg) corresponding respectively to 3.9 and 0.2 times the estimated clinical exposure (AUC_{0-24h}) at the 10 mg daily human dose.

Everolimus was not genotoxic in a battery of *in vitro* assays (Ames mutation test in *Salmonella*, mutation test in L5178Y mouse lymphoma cells, and chromosome aberration assay in V79 Chinese hamster cells). Everolimus was not genotoxic in an *in vivo* mouse bone marrow micronucleus test at doses up to 500 mg/kg/day (1500 mg/m²/day, approximately 255-fold the 10 mg daily human dose, and 103-fold the maximum dose administered to patients with SEGA, based on the body surface area), administered as two doses, 24 hours apart.

Based on non-clinical findings, male fertility may be compromised by treatment with AFINITOR. In a 13-week male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm count, and plasma testosterone levels were diminished at 5 mg/kg, which resulted in infertility at 5 mg/kg. Effects on male fertility occurred at the AUC_{0-24h} values below that of therapeutic exposure (approximately 10%-81% of the AUC_{0-24h} in patients receiving the 10 mg daily dose). After a 10-13 week non-treatment period, the fertility index increased from zero (infertility) to 60% (12/20 mated females were pregnant).

Oral doses of everolimus in female rats at ≥0.1 mg/kg (approximately 4% the AUC_{0-24h} in patients receiving the 10 mg daily dose) resulted in increases in pre-implantation loss, suggesting that the drug may reduce female fertility. Everolimus crossed the placenta and was toxic to the conceptus [see *Use in Specific Populations* (8.1)].

13.2 Animal Toxicology and/or Pharmacology

In juvenile rat toxicity studies, dose-related delayed attainment of developmental landmarks including delayed eye-opening, delayed reproductive development in males and females and increased latency time during the learning and memory phases were observed at doses as low as 0.15 mg/kg/day.

14 CLINICAL STUDIES

14.1 Advanced Neuroendocrine Tumors

Locally Advanced or Metastatic Advanced Pancreatic Neuroendocrine Tumors (PNET):

A randomized, double-blind, multi-center trial of AFINITOR plus best supportive care (BSC) versus placebo plus BSC was conducted in patients with locally advanced or metastatic advanced pancreatic neuroendocrine tumors (PNET) and disease progression within the prior 12 months. Patients were stratified by prior cytotoxic chemotherapy (yes/no) and by WHO performance status (0 vs. 1 and 2). Treatment with somatostatin analogs was allowed as part of BSC. The primary endpoint for the trial was progression-free survival (PFS) evaluated by RECIST (Response Evaluation Criteria in Solid

Tumors). After documented radiological progression, patients could be unblinded by the investigator; those randomized to placebo were then able to receive open-label AFINITOR. Other endpoints included safety, objective response rate [ORR (complete response (CR) or partial response (PR))], response duration, and overall survival.

Patients were randomized 1:1 to receive either AFINITOR 10mg/day (n=207) or placebo (n=203). Demographics were well balanced (median age 58 years, 55% male, 79% Caucasian). Crossover from placebo to open-label AFINITOR occurred in 73% (148/203) of patients.

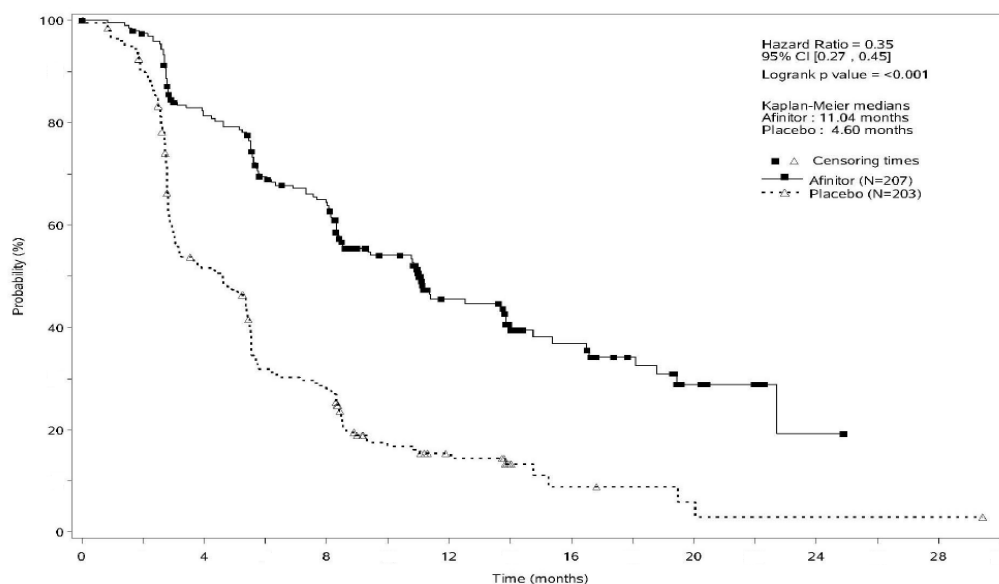
The trial demonstrated a statistically significant improvement in PFS (median 11.0 months versus 4.6 months), resulting in a 65% risk reduction in investigator-determined PFS (HR 0.35; 95%CI: 0.27 to 0.45; p<0.001) (see Table 9 and Figure 1). PFS improvement was observed across all patient subgroups, irrespective of prior somatostatin analog use. The PFS results by investigator radiological review, central radiological review and adjudicated radiological review are shown below in Table 9.

Table 9: Progression-free Survival Results

Analysis	N	AFINITOR N=207	Placebo N=203	Hazard Ratio (95%CI)	p-value
	410	Median progression-free survival (months) (95% CI)			
Investigator radiological review		11.0 (8.4 to 13.9)	4.6 (3.1 to 5.4)	0.35 (0.27 to 0.45)	<0.001
Central radiological review		13.7 (11.2 to 18.8)	5.7 (5.4 to 8.3)	0.38 (0.28 to 0.51)	<0.001
Adjudicated radiological review ^a		11.4 (10.8 to 14.8)	5.4 (4.3 to 5.6)	0.34 (0.26 to 0.44)	<0.001

^a includes adjudication for discrepant assessments between investigator radiological review and central radiological review

Figure 1: Kaplan-Meier Investigator-Determined Progression-free Survival Curves



Investigator-determined response rate was low (4.8%) in the AFINITOR arm and there were no complete responses. The overall survival results are not yet mature and no statistically significant treatment-related difference in OS was noted [HR=1.05 (95% CI: 0.71 to 1.55)].

Locally Advanced or Metastatic Carcinoid Tumors

In a randomized, double-blind, multi-center trial in 429 patients with carcinoid tumors, AFINITOR plus depot octreotide (Sandostatin LAR[®]) was compared to placebo plus depot octreotide. After documented radiological progression, patients could be unblinded by the investigator: those randomized to placebo were then able to receive open-label AFINITOR plus depot octreotide. The study did not meet the primary efficacy endpoint (PFS) and the OS interim analysis numerically favored the placebo plus depot octreotide arm. Therefore, the use of AFINITOR in patients with carcinoid tumors remains investigational.

14.2 Advanced Renal Cell Carcinoma

An international, multi-center, randomized, double-blind trial comparing AFINITOR 10 mg daily and placebo, both in conjunction with best supportive care, was conducted in patients with metastatic RCC whose disease had progressed despite prior treatment with sunitinib, sorafenib, or both sequentially. Prior therapy with bevacizumab, interleukin 2, or interferon- α was also permitted. Randomization was stratified according to prognostic score and prior anticancer therapy [see References (15)].

Progression-free survival (PFS), documented using Response Evaluation Criteria in Solid Tumors (RECIST) was assessed via a blinded, independent, central radiologic review. After documented radiological progression, patients could be unblinded by the investigator: those randomized to placebo were then able to receive open-label AFINITOR 10 mg daily.

In total, 416 patients were randomized 2:1 to receive AFINITOR (n=277) or placebo (n=139). Demographics were well balanced between the two arms (median age 61 years; 77% male, 88% Caucasian, 74% received prior sunitinib or sorafenib, and 26% received both sequentially).

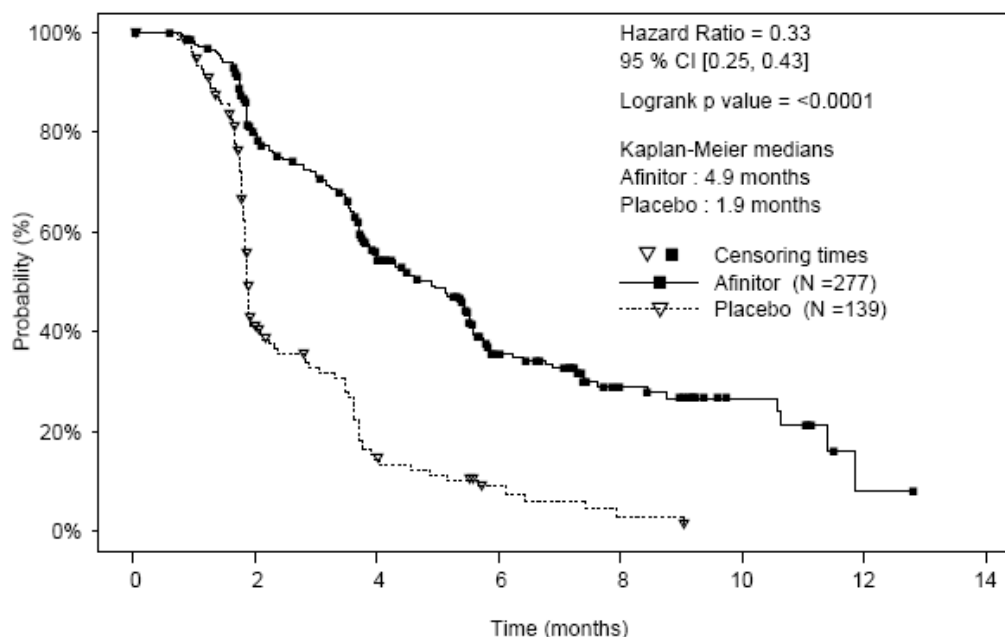
AFINITOR was superior to placebo for PFS (see Table 10 and Figure 2). The treatment effect was similar across prognostic scores and prior sorafenib and/or sunitinib. Final overall survival (OS) results yield a hazard ratio of 0.90 (95% CI: 0.71 to 1.14), with no statistically significant difference between the two treatment groups. Planned crossover from placebo due to disease progression to open label AFINITOR occurred in 111 of the 139 patients (79.9%) and may have confounded the OS benefit.

Table 10: Efficacy Results by Central Radiologic Review

	AFINITOR N=277	Placebo N=139	Hazard Ratio (95% CI)	p-value ^a
Median Progression-free Survival (95% CI)	4.9 months (4.0 to 5.5)	1.9 months (1.8 to 1.9)	0.33 (0.25 to 0.43)	<0.0001
Objective Response Rate	2%	0%	n/a ^b	n/a ^b

^a Log-rank test stratified by prognostic score.
^b Not applicable.

Figure 2: Kaplan-Meier Progression-free Survival Curves



14.3 Renal Angiomyolipoma with Tuberous Sclerosis Complex

A randomized (2:1), double-blind, placebo-controlled trial of AFINITOR was conducted in 118 patients with renal angiomyolipoma as a feature of TSC (n=113) or sporadic lymphangiomyomatosis (n=5).

The key eligibility requirements for this trial were at least one angiomyolipoma of ≥ 3 cm in longest diameter on CT/MRI based on local radiology assessment, no immediate indication for surgery, and age ≥ 18 years. Patients received daily oral AFINITOR 10 mg or matching placebo until disease progression or unacceptable toxicity. CT or MRI scans for disease

assessment were obtained at baseline, 12, 24, and 48 weeks and annually thereafter. Clinical and photographic assessment of skin lesions were conducted at baseline and every 12 weeks thereafter until treatment discontinuation. The major efficacy outcome measure was angiomyolipoma response rate based on independent central radiology review, which was defined as a $\geq 50\%$ reduction in angiomyolipoma volume, absence of new angiomyolipoma lesion ≥ 1 cm, absence of kidney volume increase $\geq 20\%$, and no angiomyolipoma related bleeding of \geq Grade 2. Key supportive efficacy outcome measures were time to angiomyolipoma progression and skin lesion response rate. Analyses of efficacy outcome measures were limited to the blinded treatment period which ended 6 months after the last patient was randomized. The comparative angiomyolipoma response rate analysis was stratified by use of enzyme-inducing antiepileptic drugs (EIAEDs) at randomization (yes/no).

Of the 118 patients enrolled, 79 were randomized to AFINITOR and 39 to placebo. The median age was 31 years (range 18 to 61 years), 34% were male, and 89% were Caucasian. At baseline, 17% of patients were receiving EIAEDs. On central radiology review at baseline, 92% of patients had at least one angiomyolipoma of ≥ 3 cm in longest diameter, 29% had angiomyolipomas ≥ 8 cm, 78% had bilateral angiomyolipomas, and 97% had skin lesions. The median values for the sum of all target renal angiomyolipoma lesions at baseline were 85 cm³ (range 9 to 1612 cm³) and 120 cm³ (range 3 to 4520 cm³) in the AFINITOR and placebo arms respectively. Forty-six (39%) patients had prior renal embolization or nephrectomy. The median duration of follow-up was 8.3 months (range 0.7 to 24.8 months).

The renal angiomyolipoma response rate was statistically significantly higher in AFINITOR-treated patients; there were 33 (41.8%) patients with angiomyolipoma responses in the AFINITOR arm as compared to none in the placebo arm. Results are displayed in Table 11. The median response duration is 5.3+ months (range 2.3+ to 19.6+ months).

Table 11: Angiomyolipoma Response

	AFINITOR N=79	Placebo N=39	p-value
Primary analysis			
Angiomyolipoma response rate^a - %	41.8	0	<0.0001
95% CI	(30.8, 53.4)	(0.0, 9.0)	

^a Per independent central radiology review

There were 3 patients in the AFINITOR arm and 8 patients in the placebo arm with documented angiomyolipoma progression by central radiologic review. The time to angiomyolipoma progression was statistically significantly longer in the AFINITOR arm (HR 0.08 [95% CI: 0.02, 0.37]; $p < 0.0001$).

Skin lesion response rates were assessed by local investigators in 77 patients in the AFINITOR arm and 37 patients in the placebo arm with skin lesions at study entry. The skin lesion response rate was statistically significantly higher in the AFINITOR arm (26% vs. 0, $p=0.0011$); all skin lesion responses were partial responses, defined as visual improvement in 50%-99% skin lesions, considering all skin lesions, durable for at least eight weeks (Physician's Global Assessment of Clinical Condition).

14.4 Subependymal Giant Cell Astrocytoma

An open-label, single-arm trial was conducted to evaluate the safety and efficacy of AFINITOR in patients with SEGA associated with TSC. Serial radiological evidence of SEGA growth was required for entry. Change in SEGA volume at the end of the core 6-month treatment phase was assessed via an independent central radiology review. In total, 28 patients received treatment with AFINITOR; median age was 11 years (range 3-34), 61% male, 86% Caucasian. Four patients had surgical resection of their SEGA lesions with subsequent re-growth prior to receiving AFINITOR treatment. After the core treatment phase, patients could continue to receive AFINITOR treatment as part of an extension treatment phase where SEGA volume was assessed every 6 months. The median duration of treatment was 24.4 months (range 4.7-37.3 months).

At 6 months, 9 out of 28 patients (32%, 95% CI: 16% to 52%) had a $\geq 50\%$ reduction in the tumor volume of their largest SEGA lesion. Duration of response for these 9 patients ranged from 97 to 946 days with a median of 266 days. Seven of these 9 patients had an ongoing volumetric reduction of $\geq 50\%$ at the data cutoff.

Three of 4 patients who had prior surgery experienced a $\geq 50\%$ reduction in the tumor volume of their largest SEGA lesion. One of these three patients responded by month 6. No patient developed new lesions.

15 REFERENCES

- Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell cancer. *J Clin Oncol* (2004) 22:454-63.

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- OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
- American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* (2006) 63:1172-93.
- Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. *Chemotherapy and biotherapy guidelines and recommendations for practice* (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

2.5 mg tablets

White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “LCL” on one side and “NVR” on the other; available in:

Blisters of 28 tablets.....NDC 0078-0594-51
 Each carton contains 4 blister cards of 7 tablets each

5 mg tablets

White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “5” on one side and “NVR” on the other; available in:

Blisters of 28 tablets.....NDC 0078-0566-51
 Each carton contains 4 blister cards of 7 tablets each

7.5 mg tablets

White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “7P5” on one side and “NVR” on the other; available in:

Blisters of 28 tablets.....NDC 0078-0620-51
 Each carton contains 4 blister cards of 7 tablets each

10 mg tablets

White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “UHE” on one side and “NVR” on the other; available in:

Blisters of 28 tablets.....NDC 0078-0567-51
 Each carton contains 4 blister cards of 7 tablets each

Store AFINITOR (everolimus) tablets at 25°C (77°F); excursions permitted between 15°–30°C (59°–86°F). See USP Controlled Room Temperature. Store in the original container, protect from light and moisture. Keep this and all drugs out of the reach of children.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published [*see References (15)*].

AFINITOR tablets should not be crushed. Do not take tablets which are crushed or broken.

17 PATIENT COUNSELING INFORMATION

17.1 Non-infectious Pneumonitis

Warn patients of the possibility of developing non-infectious pneumonitis. In clinical studies, some non-infectious pneumonitis cases have been severe and occasionally fatal. Advise patients to report promptly any new or worsening respiratory symptoms [*see Warnings and Precautions (5.1)*].

17.2 Infections

Inform patients that they are more susceptible to infections while being treated with AFINITOR and that cases of hepatitis B reactivation have been associated with AFINITOR treatment. In clinical studies, some of these infections have been severe (e.g., leading to respiratory or hepatic failure) and occasionally fatal. Patients should be aware of the signs and symptoms of infection and should report any such signs or symptoms promptly to their physician [*see Warnings and Precautions (5.2)*].

17.3 Oral Ulceration

Inform patients of the possibility of developing mouth ulcers, stomatitis, and oral mucositis. In such cases, mouthwashes and/or topical treatments are recommended, but these should not contain alcohol or peroxide [see *Warnings and Precautions (5.3)*].

17.4 Renal Failure

Inform patients of the possibility of developing kidney failure. In some cases kidney failure has been severe and occasionally fatal. Inform patients of the need for the healthcare provider to monitor kidney function, especially in patients with risk factors that may impair kidney function [see *Warnings and Precautions (5.4)*].

17.5 Laboratory Tests and Monitoring

Inform patients of the need to monitor blood chemistry and hematology prior to the start of AFINITOR therapy and periodically thereafter [see *Warnings and Precautions (5.5)*].

17.6 Drug-drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications and dietary supplements. Inform the patients to avoid concomitant administration of strong CYP3A4 inhibitors or inducers while on AFINITOR treatment [see *Dosage and Administration (2.2, 2.4)*, *Warnings and Precautions (5.6)*, *Drug Interactions (7.1, 7.2)*].

17.7 Vaccinations

Advise patients to avoid the use of live vaccines and close contact with those who have received live vaccines [see *Warnings and Precautions (5.8)*].

17.8 Pregnancy

Advise female patients of childbearing potential that AFINITOR may cause fetal harm and that an effective method of contraception should be used during therapy with AFINITOR and for 8 weeks after ending treatment.

17.9 Dosing Instructions

Inform patients to take AFINITOR orally once daily at the same time every day, either consistently with food or consistently without food. AFINITOR should be swallowed whole with a glass of water. 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.

Instruct patients that if they miss a dose of AFINITOR, they may still take it up to 6 hours after the time they would normally take it. If more than 6 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take AFINITOR at the usual time. Warn patients to not take 2 doses to make up for the one that they missed.

PATIENT INFORMATION
AFINITOR® (a-fin-it-or)
(everolimus)
tablets

Read this Patient Information leaflet that comes with AFINITOR before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about AFINITOR?

AFINITOR can cause serious side effects. These serious side effects include:

1. **You may develop lung or breathing problems.** In some people lung or breathing problems may be severe, and can even lead to death. Tell your healthcare provider right away if you have any of these symptoms:
 - New or worsening cough
 - Shortness of breath
 - Chest pain
 - Difficulty breathing or wheezing
2. **You may be more likely to develop an infection,** such as pneumonia, or a bacterial, fungal or viral infection. Viral infections may include active hepatitis B in people who have had hepatitis B in the past (reactivation). In some people these infections may be severe, and can even lead to death. You may need to be treated as soon as possible.

Tell your healthcare provider right away if you 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
- Skin rash
- Joint pain and inflammation
- Tiredness
- Loss of appetite
- Nausea
- Pale stool or dark urine
- Yellowing of the skin
- Pain in your upper right side

3. **You may develop kidney failure.** In some people this may be severe and can even lead to death. Your healthcare provider should do tests to check your kidney function before and during your treatment with AFINITOR.

If you have any of the serious side effects listed above, you may need to stop taking AFINITOR for a while or use a lower dose. Follow your healthcare provider's instructions.

What is AFINITOR?

AFINITOR is a prescription medicine used to treat:

- people with a type of pancreatic cancer known as pancreatic neuroendocrine tumor (PNET), that has progressed and can not be treated with surgery.
It is not known if AFINITOR is safe and effective in people with carcinoid tumors.

- people with advanced kidney cancer (renal cell carcinoma or RCC) when certain other medicines have not worked.
- people with the following types of tumors that are seen with a genetic condition called tuberous sclerosis complex (TSC):
 - a kidney tumor called angiomyolipoma, when their kidney tumor does not require surgery right away.
 - a brain tumor called subependymal giant cell astrocytoma (SEGA).

It is not known if AFINITOR is safe and effective in children under 3 years of age with SEGA.

Who should not take AFINITOR?

Do not take AFINITOR if you are allergic to AFINITOR or to any of its ingredients. See the end of this leaflet for a complete list of ingredients in AFINITOR. Talk to your healthcare provider before taking this medicine if you are allergic to:

- sirolimus (Rapamune[®])
- temsirolimus (Torisel[®])

Ask your healthcare provider if you do not know.

What should I tell my healthcare provider before taking AFINITOR?

Before taking AFINITOR, tell your healthcare provider about all of your medical conditions, including if you:

- Have or have had kidney problems
- Have or have had liver problems
- Have diabetes or high blood sugar
- Have high blood cholesterol levels
- Have any infections
- Previously had hepatitis B
- Are scheduled to receive any vaccinations. You should not receive a live vaccine or be around people who have recently received a live vaccine during your treatment with AFINITOR. If you are not sure about the type of immunization or vaccine, ask your healthcare provider.
- Have other medical conditions.
- Are pregnant, or could become pregnant. It is not known if AFINITOR will harm your unborn baby. You should use effective birth control while using AFINITOR and for 8 weeks after stopping treatment.
- Are breast-feeding or plan to breast-feed. It is not known if AFINITOR passes into your breast milk. You and your healthcare provider should decide if you will take AFINITOR or breast-feed. You should not do both.

Tell your healthcare provider about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

AFINITOR may affect the way other medicines work, and other medicines can affect how AFINITOR works. Using AFINITOR with other medicines can cause serious side effects.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine. Especially tell your healthcare provider if you take:

- St. John's Wort (*Hypericum perforatum*)
- Medicine for:
 - Fungal infections
 - Bacterial infections
 - Tuberculosis
 - Seizures

- HIV-AIDS
- Heart conditions or high blood pressure
- Medicines that suppress your immune system

Ask your healthcare provider or pharmacist if you are not sure if your medicine is one of those taken for the conditions listed above. If you are taking any medicines for the conditions listed above, your healthcare provider might need to prescribe a different medicine or your dose of AFINITOR may need to be changed. You should also tell your healthcare provider before you start taking any new medicine.

How should I take AFINITOR?

- Your healthcare provider will prescribe the dose of AFINITOR that is right for you.
- Take AFINITOR exactly as your healthcare provider tells you. Your healthcare provider may change your dose of AFINITOR if needed.
- Swallow AFINITOR tablets whole with a glass of water.
- If you cannot swallow AFINITOR tablets whole, you can stir them into a glass of water:
 - Put the prescribed number of tablets into a glass that contains about 2 Tablespoons (30 mL) of water
 - Gently stir the contents until the tablets break apart and then drink the mixture right away
 - Add about 2 Tablespoons (30 mL) of water to the glass and drink all of the water. This will help to make sure that you get the full dose of AFINITOR.
- Take AFINITOR one time every day, at about the same time every day.
- Take AFINITOR the same way each time, either with food or without food.
- You may use scissors to open the blister to avoid spillage.
- If you take too much AFINITOR contact your healthcare provider or go to the nearest hospital emergency department right away. Take the pack of AFINITOR with you.
- If you miss a dose of AFINITOR, you may still take it up to 6 hours after the time you normally take it. If it is more than 6 hours after you normally take your AFINITOR, skip the dose for that day. The next day, take AFINITOR at your usual time. Do not take 2 doses to make up for the one that you missed. If you are not sure about what to do, call your healthcare provider.
- You should have regular blood tests before you start AFINITOR and as needed during your treatment. These will include tests to check your blood cell count, kidney and liver function, cholesterol, and blood sugar levels.
- If you take AFINITOR to treat SEGA, you will need to have regular blood tests to measure how much AFINITOR is in your blood. This will help your healthcare provider decide how much AFINITOR you need to take.

What should I avoid while taking AFINITOR?

You should not drink grapefruit juice or eat grapefruit during your treatment with AFINITOR. It may make the amount of AFINITOR in your blood increase to a harmful level.

What are the possible side effects of AFINITOR?

AFINITOR can cause serious side effects.

- **See “What is the most important information I should know about AFINITOR?”**

Common side effects of AFINITOR in people with advanced pancreatic neuroendocrine tumors and patients with advanced kidney cancer include:

- Mouth ulcers. AFINITOR can cause mouth ulcers and sores. Tell your healthcare provider if you have pain, discomfort, or open sores in your mouth. Your healthcare provider may tell you to use a special mouthwash or mouth gel that does not contain alcohol or peroxide.
- Feeling weak or tired
- Cough, shortness of breath
- Diarrhea
- Rash, dry skin, and itching
- Nausea and vomiting
- Fever
- Loss of appetite
- Swelling of arms, hands, feet, ankles, face or other parts of the body
- Abnormal taste
- Inflammation of lining of the digestive system
- Headache
- Nose bleeds
- Pain in arms and legs

Common side effects of AFINITOR in patients who have angiomyolipoma with TSC include:

- Mouth ulcers. AFINITOR can cause mouth ulcers and sores. Tell your healthcare provider if you have pain, discomfort, or open sores in your mouth. Your healthcare provider may tell you to use a special mouthwash or mouth gel that does not contain alcohol or peroxide.
- Acne or eczema
- Nausea and vomiting
- Headache
- Cough
- Diarrhea
- Joint pain
- Swelling of your hands, arms, legs, and feet
- Stomach-area (abdomen) pain
- Respiratory tract infection
- Increased blood cholesterol level and certain other blood tests
- Decreased blood phosphate level
- Low red blood cells and white blood cells
- Increased blood sugar levels
- Absence of menstrual periods (menstruation). You may miss one or more menstrual periods. Tell your healthcare provider if this happens.

Common side effects of AFINITOR in patients with SEGA include:

- Infections of the respiratory tract, sinuses and ears
- Mouth ulcers. AFINITOR can cause mouth ulcers and sores. Tell your healthcare provider if you have pain, discomfort, or open sores in your mouth. Your healthcare provider may tell you to use a special mouthwash or mouth gel that does not contain alcohol or peroxide.
- Diarrhea and constipation
- Vomiting
- Stomach pain
- Fever
- Seizure
- Headache
- Dizziness
- Skin problems (such as rash, acne, dry skin, or scratching of the skin)
- Cough

- Stuffy or runny nose
- Change in personality
- Low white blood cells (a type of blood cell that fights infection; your healthcare provider will periodically check you for this problem)
- High levels of fats in the blood (raised triglycerides)

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

These are not all the possible side effects of AFINITOR. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store AFINITOR?

- Store AFINITOR at room temperature, between 68°F to 77°F (20°C to 25°C)
- Keep AFINITOR in the package it comes in.
- Open the blister package just before taking AFINITOR.
- Keep the blister package and tablets dry prior to taking.
- Keep AFINITOR out of light.
- Throw away AFINITOR that is out of date or no longer needed.

Keep AFINITOR and all medicines out of the reach of children.

General information about AFINITOR

Medicines are sometimes prescribed for conditions that are not mentioned in a patient information leaflet. Do not use AFINITOR for a condition for which it was not prescribed. Do not give AFINITOR to other people, even if they have the same problem you have. It may harm them.

This leaflet summarizes the most important information about AFINITOR. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information written for healthcare professionals.

For more information call 1-888-423-4648 or go to www.AFINITOR.com.

What are the ingredients in AFINITOR?

Active ingredient: everolimus.

Inactive ingredients: butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, and lactose anhydrous.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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