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
AFINITOR® DISPERZ (everolimus tablets for oral suspension)
Initial U.S. Approval: 2009

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

Dosage and Administration (2.2, 2.5)	9/2017
Warnings and Precautions, Stomatitis (5.4)	9/2017
Warnings and Precautions, Embryo-Fetal Toxicity (5.12)	9/2017

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

AFINITOR is a kinase inhibitor indicated for the treatment of:
- Postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane after failure of treatment with letrozole or anastrozole. (1.1)
- Adults with progressive neuroendocrine tumors of pancreatic origin (PNET) and adults with progressive, well-differentiated, non-functional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin that are unresectable, locally advanced or metastatic. AFINITOR is not indicated for the treatment of patients with functional carcinoid tumors. (1.2)
- Adults with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib. (1.3)
- Adults with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery. (1.4)

AFINITOR and AFINITOR DISPERZ are kinase inhibitors indicated for the treatment of:
- Pediatric and adult patients with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected. (1.5)

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

Advanced HR+ BC, advanced NET, 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/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, consider doubling the daily dose of AFINITOR using increments of 5 mg or less. (2.2)

SEGA with TSC:
- 4.5 mg/m^2 once daily; adjust dose to attain trough concentrations of 5-15 ng/mL. (2.3)
- Assess trough concentrations approximately 2 weeks after initiation of treatment, a change in dose, a change in co-administration of CYP3A4/PgP inducers or inhibitors, a change in hepatic function, or a change in dosage form between AFINITOR Tablets and AFINITOR DISPERZ. (2.3, 2.4)
- For patients with severe hepatic impairment reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ. (2.3, 2.5)
- If concomitant use of moderate inhibitors of CYP3A4/PgP is required, reduce the dose of AFINITOR Tablets or AFINITOR DISPERZ by 50%. (2.3, 2.5)
- If concomitant use of strong inducers of CYP3A4/PgP is required, double the dose of AFINITOR Tablets or AFINITOR DISPERZ. (2.3, 2.5)

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

AFINITOR Tablets: 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets (3.1)
AFINITOR DISPERZ Tablets, for oral suspension: 2 mg, 3 mg, and 5 mg tablets (3.2)

----------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)
- Angioedema: Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema. (5.3)
- Stomatitis: Stomatitis, including mouth ulcers and oral mucositis, occurs in most patients treated with AFINITOR. Initiation of topical treatment with dexamethasone mouthwash when starting AFINITOR reduces the incidence and severity of stomatitis. (5.4, 6.1)
- Renal failure: Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed. (5.5)
- Impaired wound healing: Increased risk of wound-related complications. Monitor signs and symptoms. Exercise caution in the peri-surgical period. (5.6)
- Laboratory test alterations: Elevations of serum creatinine, urinary protein, 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. (5.8)
- Vaccinations: Avoid live vaccines and close contact with those who have received live vaccines. (5.11)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.12, 8.1, 8.3)

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

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

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

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

- Strong CYP3A4/PgP inhibitors: Avoid concomitant use. (2.2, 2.5, 5.9, 7.1)
- Moderate CYP3A4/PgP inhibitors: If combination is required, use caution and reduce dose of AFINITOR. (2.2, 2.3, 2.5, 5.9, 7.1)
- Strong CYP3A4/PgP inducers: Avoid concomitant use. If combination cannot be avoided, increase dose of AFINITOR. (2.2, 2.3, 2.5, 5.9, 7.2)

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

- Lactation: Advise not to breastfeed. (8.2)
- Females and Males of Reproductive Potential: May impair fertility. (8.3)
- Hepatic impairment: For advanced HR+ BC, advanced NET, advanced RCC, or renal angiomyolipoma with TSC patients with hepatic impairment, reduce AFINITOR dose. For SEGA patients with severe hepatic impairment, reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ. (2.2, 2.3, 2.5, 5.10, 8.8)

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

Revised: 9/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
- 1.1 Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer (Advanced HR+ BC)
- 1.2 Advanced Neuroendocrine Tumors (NET)
- 1.3 Advanced Renal Cell Carcinoma (RCC)
- 1.4 Renal Angiomyolipoma with Tuberous Sclerosis Complex (TSC)
- 1.5 Subependymal Giant Cell Astrocytoma (SEGA) with Tuberous Sclerosis Complex (TSC)

2 DOSAGE AND ADMINISTRATION
- 2.1 Recommended Dose in Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer, Advanced NET, Advanced RCC, and Renal Angiomyolipoma with TSC
- 2.2 Dose Modifications in Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer, Advanced NET, Advanced RCC, and Renal Angiomyolipoma with TSC
- 2.3 Recommended Dose in SEGA with TSC
- 2.4 Therapeutic Drug Monitoring in SEGA with TSC
- 2.5 Dose Modifications in SEGA with TSC
- 2.6 Administration of AFINITOR Tablets in SEGA with TSC
- 2.7 Administration and Preparation of AFINITOR DISPERZ in SEGA with TSC

3 DOSAGE FORMS AND STRENGTHS
- 3.1 AFINITOR Tablets
- 3.2 AFINITOR DISPERZ

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
- 5.1 Non-infectious Pneumonitis
- 5.2 Infections
- 5.3 Angioedema with Concomitant Use of Angiotensin-Converting Enzyme (ACE) Inhibitors
- 5.4 Stomatitis
- 5.5 Renal Failure
- 5.6 Impaired Wound Healing
- 5.7 Geriatric Patients
- 5.8 Laboratory Tests and Monitoring
- 5.9 Drug-Drug Interactions
- 5.10 Hepatic Impairment
- 5.11 Vaccinations
- 5.12 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS
- 6.1 Clinical Study Experience in Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer
- 6.2 Clinical Study Experience in Advanced Neuroendocrine Tumors
- 6.3 Clinical Study Experience in Advanced Renal Cell Carcinoma
- 6.4 Clinical Study Experience in Renal Angiomyolipoma with Tuberous Sclerosis Complex
- 6.5 Clinical Study Experience in Subependymal Giant Cell Astrocytoma with Tuberous Sclerosis Complex
- 6.6 Postmarketing Experience

7 DRUG INTERACTIONS
- 7.1 Agents That May Increase Everolimus Blood Concentrations
- 7.2 Agents That May Decrease Everolimus Blood Concentrations
- 7.3 Drugs That May Have Their Plasma Concentrations Altered by Everolimus

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.7 Renal Impairment
- 8.8 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.6 QT/QTc Prolongation Potential

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES
- 14.1 Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer
- 14.2 Advanced Neuroendocrine Tumors
- 14.3 Advanced Renal Cell Carcinoma
- 14.4 Renal Angiomyolipoma with Tuberous Sclerosis Complex
- 14.5 Subependymal Giant Cell Astrocytoma with Tuberous Sclerosis Complex

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

AFINITOR® is indicated for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole.

1.2 Advanced Neuroendocrine Tumors (NET)

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

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

AFINITOR® is not indicated for the treatment of patients with functional carcinoid tumors *[see Clinical Studies (14.2)]*.

1.3 Advanced Renal Cell Carcinoma (RCC)

AFINITOR® is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib.

1.4 Renal Angiomyolipoma with Tuberous Sclerosis Complex (TSC)

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

1.5 Subependymal Giant Cell Astrocytoma (SEGA) with Tuberous Sclerosis Complex (TSC)

AFINITOR® Tablets and AFINITOR® DISPERZ are indicated in pediatric and adult patients with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.

2 DOSAGE AND ADMINISTRATION

AFINITOR is available in two dosage forms: tablets (AFINITOR Tablets) and tablets for oral suspension (AFINITOR DISPERZ).

- AFINITOR Tablets may be used for all approved indications.
- AFINITOR DISPERZ is approved for the treatment of patients with subependymal giant cell astrocytoma (SEGA) and tuberous sclerosis complex (TSC).

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

The recommended dose of AFINITOR Tablets is 10 mg, to be taken once daily at the same time every day. Administer either consistently with food or consistently without food *[see Clinical Pharmacology (12.3)]*. AFINITOR Tablets should be swallowed whole with a glass of water. Do not break or crush tablets.

Continue treatment until disease progression or unacceptable toxicity occurs.

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

Adverse Reactions

Management of severe or intolerable adverse reactions may require temporary dose interruption (with or without a dose reduction of AFINITOR therapy) or discontinuation. If dose reduction is required, the suggested dose is approximately 50% lower than the daily dose previously administered *[see Warnings and Precautions (5)]*.

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

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

Adverse Reaction	Severity[a]	AFINITOR Dose Adjustment[b] and Management Recommendations
Non-infectious pneumonitis	Grade 1 Asymptomatic, clinical or diagnostic observations only; intervention not indicated	No dose adjustment required. Initiate appropriate monitoring.
	Grade 2 Symptomatic, medical intervention indicated; limiting instrumental ADL[c]	Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to Grade ≤ 1. Re-initiate treatment at a lower dose. Discontinue treatment if failure to recover within 4 weeks.
	Grade 3 Severe symptoms; limiting self-care ADL[c]; O_2 indicated	Interrupt treatment until symptoms resolve to Grade ≤ 1. Rule out infection and consider treatment with corticosteroids. Consider re-initiating treatment at a lower dose. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4 Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Discontinue treatment, rule out infection, and consider treatment with corticosteroids.
Stomatitis	Grade 1 Asymptomatic or mild symptoms	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouthwash several times a day.
	Grade 2 Moderate pain; not interfering with oral intake; modified diet indicated	Temporary dose interruption until recovery to Grade ≤ 1. Re-initiate treatment at the same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤1. Re-initiate treatment at a lower dose. Manage with topical analgesic mouth treatments (e.g., benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e., triamcinolone oral paste).[d]
	Grade 3 Severe pain; interfering with oral intake	Temporary dose interruption until recovery to Grade ≤ 1. Re-initiate treatment at a lower dose. Manage with topical analgesic mouth treatments (i.e., benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e., triamcinolone oral paste).[d]

	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue treatment and treat with appropriate medical therapy.
Other non-hematologic toxicities (excluding metabolic events)	Grade 1	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor. If toxicity becomes intolerable, temporary dose interruption until recovery to Grade ≤ 1. Re-initiate treatment at the same dose. If toxicity recurs at Grade 2, interrupt treatment until recovery to Grade ≤ 1. Re-initiate treatment at a lower dose.
	Grade 3	Temporary dose interruption until recovery to Grade ≤ 1. Initiate appropriate medical therapy and monitor. Consider re-initiating treatment at a lower dose. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue treatment and treat with appropriate medical therapy.
Metabolic events (e.g. hyperglycemia, dyslipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.
	Grade 3	Temporary dose interruption. Re-initiate treatment at a lower dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue treatment and treat with appropriate medical therapy.
Thrombocytopenia (platelet count decreased)	Grade 1 (< LLN[e] - 75,000/mm^3; < LLN[e] - 75.0 x 10^9/L)	No dose adjustment required.
	Grade 2 (< 75,000 - 50,000/mm^3; < 75.0 - 50.0 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤ 1. Re-initiate treatment at the same dose.
	Grade 3 (< 50,000 - 25,000/mm^3; < 50.0 - 25.0 x 10^9/L) **OR** Grade 4 (< 25,000/mm^3; < 25.0 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤ 1. Re-initiate treatment at a lower dose.
Neutropenia (neutrophil count decreased)	Grade 1 (< LLN[e] – 1,500/mm^3; < LLN[e] – 1.5 x 10^9/L) **OR** Grade 2 (< 1,500 – 1,000/mm^3; < 1.5 – 1.0 x 10^9/L)	No dose adjustment required.
	Grade 3 (< 1,000 - 500/mm^3; < 1.0 - 0.5 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤ 2. Re-initiate treatment at the same dose.

	Grade 4 (< 500/mm^3; < 0.5 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤ 2. Re-initiate treatment at a lower dose.
Febrile neutropenia	Grade 3 ANC[f] < 1,000/mm^3 with a single temperature of > 38.3ºC (101ºF) or a sustained temperature of ≥ 38ºC (100.4ºF) for more than one hour	Temporary dose interruption until recovery to Grade ≤ 2 and no fever. Re-initiate treatment at a lower dose.
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue treatment.

[a] Severity grade description: 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms. Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

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

[c] Activities of daily living (ADL)

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

[e] Lower limit of normal (LLN)

[f] Absolute Neutrophil Count (ANC)

Hepatic Impairment

Hepatic impairment will increase the exposure to everolimus *[see Warnings and Precautions (5.10) and Use in Specific Populations (8.8)]*. 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/P-glycoprotein (PgP) Inhibitors

Avoid the use of strong CYP3A4/PgP inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) *[see Warnings and Precautions (5.9) and Drug Interactions (7.1)]*.

Use caution when co-administered with moderate CYP3A4/PgP inhibitors (e.g., amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem). If patients require co-administration of a moderate CYP3A4/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/PgP inhibitor.

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.

Strong CYP3A4/PgP Inducers

Avoid the use of concomitant strong CYP3A4/PgP inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital). If patients require co-administration of a strong CYP3A4/PgP inducer, consider doubling the daily dose of AFINITOR using increments of 5 mg or less. 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/PgP inducers. If the strong inducer is discontinued, consider a washout period of 3 to 5 days, before the AFINITOR dose is returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer *[see Warnings and Precautions (5.9) and Drug Interactions (7.2)]*.

St. John's Wort (*Hypericum perforatum*) may decrease everolimus exposure unpredictably and should be avoided.

2.3 Recommended Dose in SEGA with TSC

The recommended starting dose is 4.5 mg/m^2, once daily. The recommended starting dose for patients with severe hepatic impairment (Child-Pugh class C) or requiring moderate CYP3A4/PgP inhibitors is 2.5 mg/m^2, once daily *[see Dosage and Administration (2.5)]*. The recommended starting dose for patients requiring a concomitant strong CYP3A4 inducer is 9 mg/m^2, once daily *[see Dosage and Administration (2.5)]*. Round dose to the nearest strength of either AFINITOR Tablets or AFINITOR DISPERZ.

Do not combine AFINITOR Tablets and AFINITOR DISPERZ to achieve the desired total dose.

Use therapeutic drug monitoring to guide subsequent dosing *[see Dosage and Administration (2.4)]*. Adjust dose at 2 week intervals as needed to achieve and maintain trough concentrations of 5 to 15 ng/mL *[see Dosage and Administration (2.4, 2.5)]*.

Continue treatment until disease progression or unacceptable toxicity occurs. The optimal duration of therapy is unknown.

2.4 Therapeutic Drug Monitoring in SEGA with TSC

Monitor everolimus whole blood trough levels routinely in all patients. When possible, use the same assay and laboratory for therapeutic drug monitoring throughout treatment.

Assess trough concentrations approximately 2 weeks after initiation of treatment, a change in dose, a change in co-administration of CYP3A4/PgP inducers and/or inhibitors, a change in hepatic function, or a change in dosage form between AFINITOR Tablets and AFINITOR DISPERZ. Once a stable dose is attained, monitor trough concentrations every 3 to 6 months in patients with changing body surface area or every 6 to 12 months in patients with stable body surface area for the duration of treatment.

Titrate the dose to attain trough concentrations of 5 to 15 ng/mL.

- For trough concentrations less than 5 ng/mL, increase the daily dose by 2.5 mg (in patients taking AFINITOR Tablets) or 2 mg (in patients taking AFINITOR DISPERZ).
- For trough concentrations greater than 15 ng/mL, reduce the daily dose by 2.5 mg (in patients taking AFINITOR Tablets) or 2 mg (in patients taking AFINITOR DISPERZ).
- If dose reduction is required for patients receiving the lowest available strength, administer every other day.

2.5 Dose Modifications in SEGA with TSC

Adverse Reactions

Temporarily interrupt or permanently discontinue AFINITOR Tablets or AFINITOR DISPERZ for severe or intolerable adverse reactions. If dose reduction is required when reinitiating therapy, reduce the dose by approximately 50% *[*see *Dosage and Administration (2.2)* and *Warnings and Precautions (5)]*. If dose reduction is required for patients receiving the lowest available strength, administer every other day.

Hepatic Impairment

- Reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ by approximately 50% in patients with SEGA who have severe hepatic impairment (Child-Pugh class C) *[see Dosage and Administration (2.3)]*. Adjustment to the 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. Subsequent dosing should be based on therapeutic drug monitoring.
- Assess everolimus trough concentrations approximately 2 weeks after commencing treatment, a change in dose, or any change in hepatic function *[see Dosage and Administration (2.3, 2.4)]*.

CYP3A4/P-glycoprotein (PgP) Inhibitors

Avoid the use of concomitant strong CYP3A4/PgP inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) in patients receiving AFINITOR Tablets or AFINITOR DISPERZ *[see Warnings and Precautions (5.9) and Drug Interactions (7.1)]*.

For patients who require treatment with moderate CYP3A4/PgP inhibitors (e.g., amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem):

- Reduce the AFINITOR Tablets or AFINITOR DISPERZ dose by approximately 50%. Administer every other day if dose reduction is required for patients receiving the lowest available strength and maintain trough concentrations of 5 to 15 ng/mL *[see Dosage and Administration (2.3, 2.4)]*.
- Assess everolimus trough concentrations approximately 2 weeks after dose reduction *[see Dosage and Administration (2.3, 2.4)]*.
- Resume the dose that was used prior to initiating the CYP3A4/PgP inhibitor 2 to 3 days after discontinuation of a moderate inhibitor. Assess the everolimus trough concentration approximately 2 weeks later *[see Dosage and Administration (2.3, 2.4)]*.

Do not ingest foods or nutritional supplements (e.g., grapefruit, grapefruit juice) that are known to inhibit cytochrome P450 or PgP activity.

Strong CYP3A4/PgP Inducers

Avoid the use of concomitant strong CYP3A4/PgP inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) if alternative therapy is available *[see Warnings and Precautions (5.9) and Drug Interactions (7.2)]*. For patients who require treatment with a strong CYP3A4/PgP inducer:

- Double the dose of AFINITOR Tablets or AFINITOR DISPERZ and assess tolerability *[see Dosage and Administration (2.3)]*.
- Assess the everolimus trough concentration approximately 2 weeks after doubling the dose and adjust the dose if necessary to maintain a trough concentration of 5 to 15 ng/mL *[see Dosage and Administration (2.3, 2.4)]*.
- Return the AFINITOR Tablets or AFINITOR DISPERZ dose to that used prior to initiating the strong CYP3A4/PgP inducer if the strong inducer is discontinued, and assess the everolimus trough concentrations approximately 2 weeks later *[see Dosage and Administration (2.3, 2.4)]*.

Do not ingest foods or nutritional supplements (e.g., St. John's Wort (*Hypericum perforatum*)) that are known to induce cytochrome P450 activity.

2.6 Administration of AFINITOR Tablets in SEGA with TSC

Do not combine the 2 dosage forms (AFINITOR Tablets and AFINITOR DISPERZ) to achieve the desired total dose. Use one dosage form or the other.

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

AFINITOR Tablets should be swallowed whole with a glass of water. Do not break or crush tablets.

2.7 Administration and Preparation of AFINITOR DISPERZ in SEGA with TSC

Wear gloves to avoid possible contact with everolimus when preparing suspensions of AFINITOR DISPERZ for another person.

Do not combine the 2 dosage forms (AFINITOR Tablets and AFINITOR DISPERZ) to achieve the desired total dose. Use one dosage form or the other.

Administer AFINITOR DISPERZ (everolimus tablets for oral suspension) as a suspension only.

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

Administer suspension immediately after preparation. Discard suspension if not administered within 60 minutes after preparation.

Prepare suspension in water only.

Using an oral syringe:

- Place the prescribed dose of AFINITOR DISPERZ into a 10-mL syringe. Do not exceed a total of 10 mg per syringe. If higher doses are required, prepare an additional syringe. Do not break or crush tablets.
- Draw approximately 5 mL of water and 4 mL of air into the syringe.
- Place the filled syringe into a container (tip up) for 3 minutes, until the AFINITOR DISPERZ tablets are in suspension.
- Gently invert the syringe 5 times immediately prior to administration.
- After administration of the prepared suspension, draw approximately 5 mL of water and 4 mL of air into the same syringe, and swirl the contents to suspend remaining particles. Administer the entire contents of the syringe.

Using a small drinking glass:

- Place the prescribed dose of AFINITOR DISPERZ into a small drinking glass (maximum size 100 mL) containing approximately 25 mL of water. Do not exceed a total of 10 mg of AFINITOR DISPERZ per glass. If higher doses are required, prepare an additional glass. Do not break or crush tablets.
- Allow 3 minutes for suspension to occur.
- Stir the contents gently with a spoon, immediately prior to drinking.
- After administration of the prepared suspension, add 25 mL of water and stir with the same spoon to re-suspend remaining particles. Administer the entire contents of the glass.

3 DOSAGE FORMS AND STRENGTHS

3.1 AFINITOR Tablets

2.5 mg tablet
White to slightly yellow, elongated tablets with a bevelled edge and 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 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 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 engraved with “UHE” on one side and “NVR” on the other.

3.2 AFINITOR DISPERZ

2 mg tablet for oral suspension
White to slightly yellowish, round, flat tablets with a bevelled edge and engraved with “D2” on one side and “NVR” on the other.

3 mg tablet for oral suspension
White to slightly yellowish, round, flat tablets with a bevelled edge and engraved with “D3” on one side and “NVR” on the other.

5 mg tablet for oral suspension
White to slightly yellowish, round, flat tablets with a bevelled edge and engraved with “D5” on one side and “NVR” on the other.

4 CONTRAINDICATIONS

AFINITOR is contraindicated in patients with 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 19% of patients treated with AFINITOR in clinical trials, some cases reported with pulmonary hypertension (including pulmonary arterial hypertension) as a secondary event. The incidence of Common Terminology Criteria (CTC) Grade 3 and 4 non-infectious pneumonitis was up to 4.0% and up to 0.2%, respectively *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5)]*. 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. Opportunistic infections such as pneumocystis jiroveci pneumonia (PJP) should be considered in the differential diagnosis. 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 *[see Table 1 in Dosage and Administration (2.2)]*.

For cases of Grade 3 non-infectious pneumonitis, interrupt AFINITOR until resolution to less than or equal to Grade 1. AFINITOR may be re-introduced at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances *[see Dosage and Administration (2.2)]*. If toxicity recurs at Grade 3, consider discontinuation of AFINITOR. For cases of Grade 4 non-infectious pneumonitis, discontinue AFINITOR. Corticosteroids may be indicated until clinical symptoms resolve. For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for PJP may be considered. 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, 6.5)]*. Localized and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections, invasive fungal infections, such as aspergillosis, candidiasis, or pneumocystis jiroveci pneumonia (PJP) 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 sepsis, 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.

Pneumocystis jiroveci pneumonia, some with a fatal outcome, has been reported in patients who received everolimus. This may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

5.3 Angioedema with Concomitant Use of Angiotensin-Converting Enzyme (ACE) Inhibitors

Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment). In a pooled analysis of randomized double-blind oncology clinical trials, the incidence of angioedema in patients taking everolimus with an ACE inhibitor was 6.8% compared to 1.3% in the control arm with an ACE inhibitor.

5.4 Stomatitis

Stomatitis, including mouth ulcers and oral mucositis, has occurred in patients treated with AFINITOR at an incidence ranging from 44%-78% across the clinical trial experience. Grade 3 or 4 stomatitis was reported in 4%-9% of patients *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5)]*. Stomatitis most often occurs within the first 8 weeks of treatment. When starting AFINITOR, initiating dexamethasone alcohol-free oral solution as a swish and spit mouthwash reduces the incidence and severity of stomatitis *[see Adverse Reactions (6.1) and Use in Specific Populations (8.4)]*. If stomatitis does occur, mouthwashes and/or other topical treatments are recommended, but alcohol-, hydrogen peroxide-, iodine-, or thyme- containing products should be avoided as they may exacerbate the condition *[see Dosage and Administration (2.2)]*. Antifungal agents should not be used unless fungal infection has been diagnosed *[see Drug Interactions (7.1)]*.

5.5 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 (5.8)]*.

5.6 Impaired Wound Healing

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

5.7 Geriatric Patients

In the randomized advanced hormone receptor-positive, HER2-negative breast cancer study (BOLERO-2), the incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients ≥ 65 years of age compared to 2% in patients < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% in patients < 65 years of age. Careful monitoring and appropriate dose adjustments for adverse reactions are recommended *[see Dosage and Administration (2.2), Use in Specific Populations (8.5)]*.

5.8 Laboratory Tests and Monitoring

Renal Function

Elevations of serum creatinine and proteinuria have been reported in patients taking AFINITOR *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5)]*. 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. Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function.

Blood Glucose and Lipids

Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported in patients taking AFINITOR *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5)]*. Monitoring of fasting serum glucose and lipid profile is recommended prior to the start of AFINITOR therapy and periodically thereafter as well as management with appropriate medical therapy. More frequent monitoring is recommended when AFINITOR is co-administered with other drugs that may induce hyperglycemia. 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 patients taking AFINITOR *[see Adverse Reactions (6.1, 6.2, 6.3, 6.4, 6.5)]*. Monitoring of complete blood count is recommended prior to the start of AFINITOR therapy and periodically thereafter.

5.9 Drug-Drug Interactions

Due to significant increases in exposure of everolimus, co-administration with strong CYP3A4/PgP inhibitors should be avoided *[see Dosage and Administration (2.2, 2.5) and Drug Interactions (7.1)]*.

A reduction of the AFINITOR dose is recommended when co-administered with a moderate CYP3A4/PgP inhibitor *[see Dosage and Administration (2.2, 2.5) and Drug Interactions (7.1)]*.

An increase in the AFINITOR dose is recommended when co-administered with a strong CYP3A4/PgP inducer *[see Dosage and Administration (2.2, 2.5) and Drug Interactions (7.2)]*.

5.10 Hepatic Impairment

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

For advanced HR+ BC, advanced NET, 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 patients with SEGA and mild or moderate hepatic impairment, adjust the dose of AFINITOR Tablets or AFINITOR DISPERZ based on therapeutic drug monitoring. For patients with SEGA and severe hepatic impairment, reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ by approximately 50% and adjust subsequent doses based on therapeutic drug monitoring *[see Dosage and Administration (2.4, 2.5)]*.

5.11 Vaccinations

During AFINITOR treatment, avoid the use of live vaccines and avoid close contact with individuals who have received live vaccines (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines).

For pediatric patients with SEGA that do not require immediate treatment, complete the recommended childhood series of live virus vaccinations according to American Council on Immunization Practices (ACIP) guidelines prior to the start of therapy. An accelerated vaccination schedule may be appropriate.

5.12 Embryo-Fetal Toxicity

Based on animal studies and the mechanism of action *[see Clinical Pharmacology (12.1)]*, AFINITOR can cause fetal harm when administered to a pregnant woman. In animal studies, everolimus caused embryo-fetal toxicities in rats when administered during the period of organogenesis at maternal exposures that were lower than human exposures at the clinical dose of 10 mg daily. Advise pregnant women of the potential risk to a fetus.

Advise female patients of reproductive potential to avoid becoming pregnant and to use effective contraception during treatment with AFINITOR and for 8 weeks after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with AFINITOR and for 4 weeks after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

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)]*.
- Angioedema with concomitant use of ACE inhibitors *[see Warnings and Precautions (5.3)]*.
- Stomatitis *[see Warnings and Precautions (5.4)]*.
- Renal failure *[see Warnings and Precautions (5.5)]*.
- Impaired wound healing *[see Warnings and Precautions (5.6)]*.

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 Hormone Receptor-Positive, HER2-Negative Breast Cancer

The efficacy and safety of AFINITOR (10 mg/day) plus exemestane (25 mg/day) (n=485) versus placebo plus exemestane (25 mg/day) (n=239) was evaluated in a randomized, controlled trial (BOLERO-2) in patients with advanced or metastatic hormone receptor-positive, HER2-negative breast cancer. The median age of patients was 61 years (range 28-93 years), and 75% were Caucasian. Safety results are based on a median follow-up of approximately 13 months.

The most common adverse reactions (incidence ≥ 30%) were stomatitis, infections, rash, fatigue, diarrhea, and decreased appetite. The most common Grade 3/4 adverse reactions (incidence ≥ 2%) were stomatitis, infections, hyperglycemia, fatigue, dyspnea, pneumonitis, and diarrhea. The most common laboratory abnormalities (incidence ≥ 50%) were hypercholesterolemia, hyperglycemia, increased aspartate transaminase (AST), anemia, leukopenia, thrombocytopenia, lymphopenia, increased alanine transaminase (ALT), and hypertriglyceridemia. The most common Grade 3/4 laboratory abnormalities (incidence ≥ 3%) were lymphopenia, hyperglycemia, anemia, decreased potassium, increased AST, increased ALT, and thrombocytopenia.

Fatal adverse reactions occurred more frequently in patients who received AFINITOR plus exemestane (2%) compared to patients on the placebo plus exemestane arm (0.4%). The rates of treatment-emergent adverse events resulting in permanent discontinuation were 24% and 5% for the AFINITOR plus exemestane and placebo plus exemestane treatment groups, respectively. Dose adjustments (interruptions or reductions) were more frequent among patients in the AFINITOR plus exemestane arm than in the placebo plus exemestane arm (63% versus 14%).

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

Table 2: Adverse Reactions Reported ≥ 10% of Patients with Advanced HR+ BC*

	AFINITOR (10 mg/day) + exemestane[a] N=482			Placebo + exemestane[a] N=238		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Any adverse reaction	**100**	**41**	**9**	**90**	**22**	**5**
Gastrointestinal disorders						
Stomatitis[b]	67	8	0	11	0.8	0
Diarrhea	33	2	0.2	18	0.8	0
Nausea	29	0.2	0.2	28	1	0
Vomiting	17	0.8	0.2	12	0.8	0
Constipation	14	0.4	0	13	0.4	0
Dry mouth	11	0	0	7	0	0
General disorders and administration site conditions						
Fatigue	36	4	0.4	27	1	0
Edema peripheral	19	1	0	6	0.4	0
Pyrexia	15	0.2	0	7	0.4	0
Asthenia	13	2	0.2	4	0	0
Infections and infestations						
Infections[c]	50	4	1	25	2	0
Investigations						
Weight decreased	25	1	0	6	0	0
Metabolism and nutrition disorders						
Decreased appetite	30	1	0	12	0.4	0
Hyperglycemia	14	5	0.4	2	0.4	0
Musculoskeletal and connective tissue disorders						
Arthralgia	20	0.8	0	17	0	0
Back pain	14	0.2	0	10	0.8	0
Pain in extremity	9	0.4	0	11	2	0
Nervous system disorders						
Dysgeusia	22	0.2	0	6	0	0
Headache	21	0.4	0	14	0	0
Psychiatric disorders						
Insomnia	13	0.2	0	8	0	0

Respiratory, thoracic and mediastinal disorders						
Cough	24	0.6	0	12	0	0
Dyspnea	21	4	0.2	11	0.8	0.4
Epistaxis	17	0	0	1	0	0
Pneumonitis[d]	19	4	0.2	0.4	0	0
Skin and subcutaneous tissue disorders						
Rash	39	1	0	6	0	0
Pruritus	13	0.2	0	5	0	0
Alopecia	10	0	0	5	0	0
Vascular disorders						
Hot flush	6	0	0	14	0	0
Median duration of treatment[e]	**23.9 weeks**			**13.4 weeks**		

Grading according to CTCAE Version 3.0

*160 patients (33.2%) were exposed to AFINITOR therapy for a period of ≥ 32 weeks

[a] Exemestane (25 mg/day)

[b] Includes stomatitis, mouth ulceration, aphthous stomatitis, glossodynia, gingival pain, glossitis and lip ulceration

[c] Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (10%), urinary tract infection (10%), upper respiratory tract infection (5%), pneumonia (4%), bronchitis (4%), cystitis (3%), sinusitis (3%), and also including candidiasis (< 1%), and sepsis (< 1%), and hepatitis C (< 1%).

[d] Includes pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis

[e] Exposure to AFINITOR or placebo

Key observed laboratory abnormalities are presented in Table 3.

Table 3: Key Laboratory Abnormalities Reported in ≥ 10% of Patients with Advanced HR+ BC

Laboratory parameter	**AFINITOR (10 mg/day) + exemestane[a] N=482**			**Placebo + exemestane[a] N=238**		
	All Grades %	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Hematology[b]						
Hemoglobin decreased	68	6	0.6	40	0.8	0.4
WBC decreased	58	1	0	28	5	0.8
Platelets decreased	54	3	0.2	5	0	0.4
Lymphocytes decreased	54	11	0.6	37	5	0.8
Neutrophils decreased	31	2	0	11	0.8	0.8
Clinical chemistry						
Glucose increased	69	9	0.4	44	0.8	0.4
Cholesterol increased	70	0.6	0.2	38	0.8	0.8
Aspartate transaminase (AST) increased	69	4	0.2	45	3	0.4
Alanine transaminase (ALT) increased	51	4	0.2	29	5	0
Triglycerides increased	50	0.8	0	26	0	0
Albumin decreased	33	0.8	0	16	0.8	0
Potassium decreased	29	4	0.2	7	1	0
Creatinine increased	24	2	0.2	13	0	0

Grading according to CTCAE Version 3.0

[a] Exemestane (25 mg/day)

[b] Reflects corresponding adverse drug reaction reports of anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia (collectively as pancytopenia), which occurred at lower frequency.

Topical Prophylaxis for Stomatitis

In a single arm study (SWISH; N=92) in postmenopausal women with hormone receptor-positive, HER2-negative breast cancer beginning AFINITOR (10 mg/day) plus exemestane (25 mg/day), patients started dexamethasone 0.5mg/5mL alcohol-free mouthwash (10 mL swished for 2 minutes and spat, 4 times daily for 8 weeks) concurrently with AFINITOR and exemestane. No food or drink was to be consumed for at least 1 hour after swishing and spitting the dexamethasone mouthwash. The primary objective of this study was to assess the incidence of Grade ≥ 2 stomatitis within 8 weeks. The incidence of Grade ≥ 2 stomatitis within 8 weeks was 2%, which was lower than the 33% reported in the BOLERO-2 trial. The incidence of Grade 1 stomatitis was 19%. No cases of Grade 3 or 4 stomatitis were reported. Oral candidiasis was reported in 2% of patients in this study compared to 0.2% in the BOLERO-2 trial.

6.2 Clinical Study Experience in Advanced Neuroendocrine Tumors

Advanced Pancreatic Neuroendocrine Tumors (PNET)

In a randomized, controlled trial (RADIANT-3) 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 White, 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 ≥ 30%) were stomatitis, rash, diarrhea, fatigue, edema, abdominal pain, nausea, fever, and headache. The most common Grade 3-4 adverse reactions (incidence ≥ 5%) were stomatitis and diarrhea. The most common laboratory abnormalities (incidence ≥ 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 ≥ 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 seven patients on AFINITOR and one 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 one death due to pulmonary embolism on the placebo arm. After cross-over to open-label AFINITOR, there were three additional deaths, one due to hypoglycemia and cardiac arrest in a patient with insulinoma, one due to myocardial infarction with congestive heart failure, 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 six patients in the everolimus arm and three patients in the placebo arm. Thrombotic events included five patients with pulmonary embolus in the everolimus arm and one in the placebo arm as well as three patients with thrombosis in the everolimus arm and two in the placebo arm.

Table 4 compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥ 10% for patients receiving AFINITOR 10 mg daily versus placebo.

Table 4: Adverse Reactions Reported ≥ 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						
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**	

Grading according to CTCAE Version 3.0

[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.

In female patients aged 18 to 55 years, irregular menstruation occurred in 5 of 46 (11%) AFINITOR-treated females and none of the 33 females in the placebo group.

Key observed laboratory abnormalities are presented in Table 5.

Table 5: Key Laboratory Abnormalities Reported in ≥ 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

Grading according to CTCAE Version 3.0

Unresectable, Locally Advanced or Metastatic, Well-Differentiated, Non-Functional Neuroendocrine Tumors of Gastrointestinal or Lung Origin

In a randomized, controlled trial (RADIANT-4) of AFINITOR (n=202 treated) versus placebo (n=98 treated) in patients with advanced non-functional NET of GI or lung origin, the median age of patients was 63 years (range 22-86), 76% were White, and 53% were female. The median duration of exposure to AFINITOR was 9.3 months; 64% of patients were treated for ≥ 6 months and 39% were treated for ≥ 12 months. AFINITOR was discontinued for adverse reactions in 29% of patients, dose reduction or delay was required in 70% of AFINITOR-treated patients.

Serious adverse reactions occurred in 42% of AFINITOR-treated patients and included 3 fatal events (cardiac failure, respiratory failure, and septic shock).

Table 6 and Table 7 summarize the incidence of adverse reactions of AFINITOR occurring at an incidence of ≥ 10% and at ≥ 5% absolute incidence over placebo (all Grades) or ≥ 2% higher incidence over placebo (Grade 3 and 4).

Table 6: Adverse Reactions in ≥ 10% of AFINITOR-Treated Patients with Non-Functional NET of Gastrointestinal or Lung Origin[†]

	AFINITOR N=202			Placebo N=98		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Any adverse reaction	**99**	**57**	**12**	**89**	**21**	**7**
Gastrointestinal disorders						
Stomatitis[a]	63	9	0	22	0	0
Diarrhea	41	8	1	31	2	0
Nausea	26	3	1	17	1	0
Vomiting	15	4	0	12	2	0
General disorders and administration site conditions						
Peripheral edema	39	3	0	6	1	0
Fatigue	37	4	1	36	1	0
Asthenia	23	2	1	8	0	0
Pyrexia	23	1	1	8	0	0
Infections						
Infections[b]	58	8	3	29	1	1
Investigations						
Decreased weight	22	2	0	11	1	0
Metabolism and nutrition disorders						
Decreased appetite	22	1	0	17	1	0
Nervous system disorders						
Dysgeusia	18	1	0	4	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	27	0	0	20	0	0
Dyspnea	20	3	0	11	1	1
Pneumonitis[c]	16	2	0	2	0	0
Epistaxis	13	1	0	3	0	0
Skin and subcutaneous disorders						
Rash	30	1	0	9	0	0
Pruritus	17	1	0	9	0	0

[†] Grading according to NCI CTCAE Version 4.03
[a] Includes stomatitis, mouth ulceration, aphthous stomatitis, gingival pain, glossitis, tongue ulceration and mucosal inflammation.
[b] Urinary tract infection, nasopharyngitis, upper respiratory tract infection, lower respiratory tract infection (pneumonia, bronchitis), abscess, pyelonephritis, septic shock and viral myocarditis.
[c] Includes pneumonitis and interstitial lung disease.

Table 7: Laboratory Abnormalities in ≥ 10% of AFINITOR-Treated Patients with Non-Functional NET of Gastrointestinal or Lung Origin†

	AFINITOR N=202			Placebo N=98		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Hematology						
Anemia	81	5	0	41	2	0
Lymphopenia	66	15	2	32	2	0
Leukopenia	49	2	0	17	0	0
Thrombocytopenia	33	2	1	11	0	0
Neutropenia	32	2	0	15	3	0
Clinical chemistry						
Hypercholesterolemia	71	0	0	37	0	0
Elevated Aspartate transaminase (AST)	57	1	1	34	2	0
Hyperglycemia (fasting)	55	6	0	36	1	0
Elevated Alanine transaminase (ALT)	46	5	1	39	1	0
Hypophosphatemia	43	4	0	15	2	0
Hypertriglyceridemia	30	3	1	8	1	0
Hypokalemia	27	4	2	12	3	0
Hypoalbuminemia	18	0	0	8	0	0

† Grading according to NCI CTCAE Version 4.03

6.3 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 (RECORD-1) 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 days) for patients receiving AFINITOR and 60 days (range 21-295 days) for those receiving placebo.

The most common adverse reactions (incidence ≥ 30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common Grade 3-4 adverse reactions (incidence ≥ 3%) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities (incidence ≥ 50%) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common Grade 3-4 laboratory abnormalities (incidence ≥ 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 8 compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥ 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 8: 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

	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
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**	

Grading according to CTCAE Version 3.0

[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%), onychoclasis (4%), skin lesion (4%), acneiform dermatitis (3%), angioedema (< 1%)

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 9.

Table 9: 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

Grading according to CTCAE Version 3.0

[a] Reflects corresponding adverse drug reaction reports of anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia (collectively pancytopenia), which occurred at lower frequency.

6.4 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 (EXIST-2) of AFINITOR in 118 patients with renal angiomyolipoma as a feature of TSC (n=113) or sporadic lymphangioleiomyomatosis (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 ≥ 30%) was stomatitis. The most common Grade 3-4 adverse reactions (incidence ≥ 2%) were stomatitis and amenorrhea. The most common laboratory abnormalities (incidence ≥ 50%) were hypercholesterolemia, hypertriglyceridemia, and anemia. The most common Grade 3-4 laboratory abnormality (incidence ≥ 3%) was hypophosphatemia.

The rate of adverse reactions 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 10 compares the incidence of adverse reactions reported with an incidence of ≥ 10% for patients receiving AFINITOR and occurring more frequently with AFINITOR than with placebo. Laboratory abnormalities are described separately in Table 11.

Table 10: Adverse Reactions Reported in ≥ 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**
Gastrointestinal disorders						
Stomatitis[a]	78	6	0	23	0	0
Vomiting	15	0	0	5	0	0
Diarrhea	14	0	0	5	0	0
General disorders and administration site conditions						
Peripheral edema	13	0	0	8	0	0
Infections and infestations						
Upper respiratory tract infection	11	0	0	5	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	13	0	0	5	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	20	0	0	13	0	0
Skin and subcutaneous tissue disorders						
Acne	22	0	0	5	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%).

The following additional adverse reactions occurred in less than 10% of AFINITOR-treated patients: epistaxis (9%), decreased appetite (6%), otitis media (6%), depression (5%), abnormal taste (5%), increased blood luteinizing hormone (LH) levels (4%), increased blood follicle stimulating hormone (FSH) levels (3%), hypersensitivity (3%), ovarian cyst (3%), pneumonitis (1%), and angioedema (1%).

Table 11: 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
Clinical chemistry						
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

Updated safety information from 112 patients treated with AFINITOR for a median duration of 3.9 years identified the following additional adverse reactions and key laboratory abnormalities: increased partial thromboplastin time (63%), increased prothrombin time (40%), decreased fibrinogen (38%), urinary tract infection (31%), proteinuria (18%), abdominal pain (16%), pruritus (12%), gastroenteritis (12%), myalgia (11%), and pneumonia (10%).

6.5 Clinical Study Experience in Subependymal Giant Cell Astrocytoma with Tuberous Sclerosis Complex

The data described below are based on a randomized (2:1), double-blind, placebo-controlled trial (EXIST-1) of AFINITOR in 117 patients with subependymal giant cell astrocytoma (SEGA) and tuberous sclerosis complex (TSC). The median age of patients was 9.5 years (range 0.8 to 26 years), 93% were Caucasian, and 57% were male. The median duration of blinded study treatment was 52 weeks (range 24 to 89 weeks) for patients receiving AFINITOR and 47 weeks (range 14 to 88 weeks) for those receiving placebo.

The most common adverse reactions reported for AFINITOR (incidence ≥ 30%) were stomatitis and respiratory tract infection. The most common Grade 3-4 adverse reactions (incidence ≥ 2%) were stomatitis, pyrexia, pneumonia, gastroenteritis, aggression, agitation, and amenorrhea. The most common key laboratory abnormalities (incidence ≥ 50%) were hypercholesterolemia and elevated partial thromboplastin time. The most common Grade 3-4 laboratory abnormality (incidence ≥ 3%) was neutropenia.

There were no adverse reactions resulting in permanent discontinuation. Dose adjustments (interruptions or reductions) due to adverse reactions occurred in 55% of AFINITOR-treated patients. The most common adverse reaction leading to AFINITOR dose adjustment was stomatitis.

Table 12 compares the incidence of adverse reactions reported with an incidence of ≥ 10% for patients receiving AFINITOR and occurring more frequently with AFINITOR than with placebo. Laboratory abnormalities are described separately in Table 13.

Table 12: Adverse Reactions Reported in ≥ 10% of AFINITOR-treated Patients with SEGA in EXIST-1

	AFINITOR N=78			**Placebo N=39**		
	All Grades	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
	%	**%**	**%**	**%**	**%**	**%**
Any adverse reaction	**97**	**36**	**3**	**92**	**23**	**3**
Gastrointestinal disorders						
Stomatitis[a]	62	9	0	26	3	0
Vomiting	22	1	0	13	0	0
Diarrhea	17	0	0	5	0	0
Constipation	10	0	0	3	0	0
Infections and infestations						
Respiratory tract infection[b]	31	1	1	23	0	0
Gastroenteritis[c]	10	4	1	3	0	0
Pharyngitis streptococcal	10	0	0	3	0	0
General disorders and administration site conditions						
Pyrexia	23	6	0	18	3	0
Fatigue	14	0	0	3	0	0
Psychiatric disorders						
Anxiety, aggression or other behavioral disturbance[d]	21	5	0	3	0	0

Skin and subcutaneous tissue disorders						
Rash[e]	21	0	0	8	0	0
Acne	10	0	0	5	0	0

Grading according to CTCAE Version 3.0
[a] Includes mouth ulceration, stomatitis, and lip ulceration
[b] Includes respiratory tract infection, upper respiratory tract infection, and respiratory tract infection viral
[c] Includes gastroenteritis, gastroenteritis viral, and gastrointestinal infection
[d] Includes agitation, anxiety, panic attack, aggression, abnormal behavior, and obsessive compulsive disorder
[e] Includes rash, rash generalized, rash macular, rash maculo-papular, rash papular, dermatitis allergic, and urticaria

Amenorrhea occurred in 17% of AFINITOR-treated females aged 10 to 55 years (3 of 18) and none of the females in the placebo group. For this same group of AFINITOR-treated females, the following menstrual abnormalities were reported: dysmenorrhea (6%), menorrhagia (6%), metrorrhagia (6%), and unspecified menstrual irregularity (6%).

The following additional adverse reactions occurred in less than 10% of AFINITOR-treated patients: nausea (8%), pain in extremity (8%), insomnia (6%), pneumonia (6%), epistaxis (5%), hypersensitivity (3%), increased blood luteinizing hormone (LH) levels (1%) and pneumonitis (1%).

Table 13: Key Laboratory Abnormalities Reported in AFINITOR-treated Patients with SEGA in EXIST-1

	AFINITOR N=78			**Placebo N=39**		
	All Grades %	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Hematology						
Elevated partial thromboplastin time	72	3	0	44	5	0
Neutropenia	46	9	0	41	3	0
Anemia	41	0	0	21	0	0
Clinical chemistry						
Hypercholesterolemia	81	0	0	39	0	0
Elevated aspartate transaminase (AST)	33	0	0	0	0	0
Hypertriglyceridemia	27	0	0	15	0	0
Elevated alanine transaminase (ALT)	18	0	0	3	0	0
Hypophosphatemia	9	1	0	3	0	0

Grading according to CTCAE Version 3.0

Updated safety information from 111 patients treated with AFINITOR for a median duration of 47 months identified the following additional notable adverse reactions and key laboratory abnormalities: decreased appetite (14%), hyperglycemia (13%), hypertension (11%), urinary tract infection (9%), decreased fibrinogen (8%), cellulitis (6%), abdominal pain (5%), decreased weight (5%), elevated creatinine (5%), and azospermia (1%).

6.6 Postmarketing Experience

The following adverse reactions have been identified during post approval use of AFINITOR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate frequency or establish a causal relationship to drug exposure: acute pancreatitis, cholecystitis, cholelithiasis, arterial thrombotic events, reflex sympathetic dystrophy, and cardiac failure with some cases reported with pulmonary hypertension (including pulmonary arterial hypertension) as a secondary event.

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/PgP should not be used *[see Dosage and Administration (2.2, 2.5) and Warnings and Precautions (5.9)]*.

Use caution when AFINITOR is used in combination with moderate CYP3A4/PgP inhibitors. If alternative treatment cannot be administered reduce the AFINITOR dose *[see Dosage and Administration (2.2, 2.5) and Warnings and Precautions (5.9)]*.

7.2 Agents That May Decrease Everolimus Blood Concentrations

CYP3A4/PgP Inducers

In healthy subjects, co-administration of AFINITOR with rifampin, a strong inducer of CYP3A4 and an inducer of PgP, 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/PgP inducers if alternative treatment cannot be administered. St. John's Wort may decrease everolimus exposure unpredictably and should be avoided *[see Dosage and Administration (2.2, 2.5)]*.

7.3 Drugs That May Have Their Plasma Concentrations 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 $AUC_{(0\text{-inf})}$.

Co-administration of everolimus and exemestane increased exemestane C_{min} by 45% and C_{2h} by 64%. However, the corresponding estradiol levels at steady state (4 weeks) were not different between the 2 treatment arms. No increase in adverse events related to exemestane was observed in patients with hormone receptor-positive, HER2-negative advanced breast cancer receiving the combination.

Co-administration of everolimus and depot octreotide increased octreotide C_{min} by approximately 50%.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal studies and the mechanism of action *[see Clinical Pharmacology (12.1)]*, AFINITOR can cause fetal harm when administered to a pregnant woman. There are limited case reports of AFINITOR use in pregnant women. However, these reports are not sufficient to inform about risks of birth defects or miscarriage. In animal studies, everolimus caused embryo-fetal toxicities in rats when administered during the period of organogenesis at maternal exposures that were lower than human exposures at the clinical dose of 10 mg daily *[see Data]*. Advise pregnant women of the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage is 2-4% and 15-20% of clinically recognized pregnancies, respectively.

Data

Animal Data

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 in rats occurred at doses ≥ 0.1 mg/kg (0.6 mg/m^2) with resulting exposures of approximately 4% of the exposure (AUC_{0-24h}) achieved in patients receiving the 10 mg daily dose of everolimus. In rabbits, embryotoxicity evident as an increase in resorptions occurred at an oral dose of 0.8 mg/kg (9.6 mg/m^2), approximately 1.6 times either the 10 mg daily dose or the median 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 the dose of 0.1 mg/kg (0.6 mg/m^2), there were no adverse effects on delivery and lactation or signs of maternal toxicity; however, there were reductions in body weight (up to 9% reduction from the control) and in survival of 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.

8.2 Lactation

Risk Summary

There are no data on the presence of everolimus in human milk, the effects of everolimus on the breastfed infant or on milk production. Everolimus and/or its metabolites passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Because of the potential for serious adverse reactions in breastfed infants from everolimus, advise lactating women not to breastfeed during treatment with AFINITOR and for 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

AFINITOR can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to seek counseling on fertility and family planning options prior to starting treatment with AFINITOR.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment and for 8 weeks after the last dose of AFINITOR *[see Use in Specific Populations (8.1)]*.

Males

Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 4 weeks after the last dose of AFINITOR *[see Use in Specific Populations (8.1)]*.

Infertility

Females

Menstrual irregularities, secondary amenorrhea, and increases in luteinizing hormone (LH) and follicle stimulating hormone (FSH) occurred in female patients taking AFINITOR. Based on these clinical findings and findings in animals, female fertility may be compromised by treatment with AFINITOR *[see Adverse Reactions (6.2, 6.4, 6.5) and Nonclinical Toxicology (13.1)]*.

Males

Based on the clinical findings and findings in animals, AFINITOR treatment may impair fertility in male patients. Cases of reversible azoospermia have been reported in male patients taking AFINITOR. In male rats, sperm motility, sperm count, plasma testosterone levels and fertility were diminished at exposures (AUC) similar to those in patients receiving a dose of 10 mg daily. The fertility index in rats increased when everolimus administration was stopped for a 10-13 week recovery period *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Pediatric use of AFINITOR Tablets and AFINITOR DISPERZ is recommended for patients 1 year of age and older with TSC for the treatment of SEGA that requires therapeutic intervention but cannot be curatively resected. The safety and effectiveness of AFINITOR Tablets and AFINITOR DISPERZ have not been established in pediatric patients with renal angiomyolipoma with TSC in the absence of SEGA.

The effectiveness of AFINITOR in pediatric patients with SEGA was demonstrated in two clinical trials based on demonstration of durable objective response, as evidenced by reduction in SEGA tumor volume *[see Clinical Studies (14.5)]*.

EXIST-1 was a randomized, double-blind, multicenter trial comparing AFINITOR (n=78) to placebo (n=39) in pediatric and adult patients. The median age was 9.5 years (range 0.8 to 26 years). At the time of randomization, a total of 20 patients were < 3 years of age, 54 patients were 3 to < 12 years of age, 27 patients were 12 to < 18 years of age, and 16 patients were ≥ 18 years of age. The overall nature, type, and frequency of adverse reactions across the age groups evaluated were similar, with the exception of a higher per patient incidence of infectious serious adverse events in patients < 3 years of age. A total of 6 of 13 patients (46%) < 3 years of age had at least 1 serious adverse event due to infection, compared to 2 of 7 patients (29%) treated with placebo. No patient in any age group discontinued AFINITOR due to infection *[see Adverse Reactions (6.5)]*. Subgroup analyses showed reduction in SEGA volume with AFINITOR treatment in all pediatric age subgroups.

Study 2485 was an open-label, single-arm, single-center trial of AFINITOR (N=28) in patients aged ≥ 3 years; median age was 11 years (range 3 to 34 years). A total of 16 patients were 3 to < 12 years, 6 patients were 12 to < 18 years, and 6 patients were ≥ 18 years. The frequency of adverse reactions across the age groups was generally similar *[see Adverse Reactions (6.5)]*. Subgroup analyses showed reductions in SEGA volume with AFINITOR treatment in all pediatric age subgroups.

Although a conclusive determination cannot be made due to the limited number of patients and lack of a comparator arm in the open label follow-up periods of EXIST-1 and Study 2485, AFINITOR did not appear to adversely impact growth and pubertal development in the 115 pediatric patients treated with AFINITOR for a median duration of 4.1 years.

Everolimus clearance normalized to body surface area was higher in pediatric patients than in adults with SEGA *[see Clinical Pharmacology (12.3)]*. The recommended starting dose and subsequent requirement for therapeutic drug monitoring to achieve and maintain trough concentrations of 5 to 15 ng/mL are the same for adult and pediatric patients with SEGA *[see Dosage and Administration (2.3, 2.4)]*.

Co-administration of AFINITOR and dexamethasone alcohol-free oral solution has not been studied in pediatric patients *[see Adverse Reactions (6.1)]*.

8.5 Geriatric Use

In the randomized advanced hormone receptor positive, HER2-negative breast cancer study (BOLERO-2), 40% of AFINITOR-treated patients were ≥ 65 years of age, while 15% were 75 years and over. No overall differences in effectiveness were observed between elderly and younger patients. The incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients ≥ 65 years of age compared to 2% in patients < 65 years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients ≥ 65 years of age compared to 17% in patients < 65 years of age *[see Warnings and Precautions (5.7)]*.

In two other randomized trials (advanced renal cell carcinoma and advanced neuroendocrine tumors of pancreatic origin), no overall differences in safety or effectiveness were observed between elderly and younger patients. In the randomized advanced RCC study (RECORD-1), 41% of AFINITOR treated patients were ≥ 65 years of age, while 7% were 75 years and over. In the randomized advanced PNET study (RADIANT-3), 30% of AFINITOR-treated patients were ≥ 65 years of age, while 7% were 75 years and over.

Other reported clinical experience has not identified differences in response 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 in initial dosing is required in elderly patients, but close monitoring and appropriate dose adjustments for adverse reactions is recommended *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

8.7 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)]*.

8.8 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 HR+ BC, advanced NET, 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 patients with SEGA who have severe hepatic impairment (Child-Pugh class C), reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ by approximately 50%. For patients with SEGA who have mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, adjustment to the starting dose may not be needed. Subsequent dosing should be 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 was observed in either mice or rats given single oral doses of 2000 mg/kg (limit test).

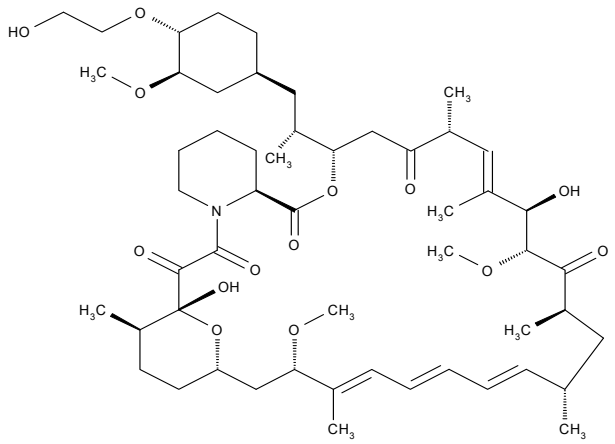
Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been administered. The acute toxicity profile observed with the 70 mg dose was consistent with that for the 10 mg dose.

11 DESCRIPTION

AFINITOR (everolimus), an inhibitor of mammalian target of rapamycin (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-dioxa-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 $C_{53}H_{83}NO_{14}$ and the molecular weight is 958.2. The structural formula is:



AFINITOR Tablets are supplied for oral administration and contain 2.5 mg, 5 mg, 7.5 mg, or 10 mg of everolimus. The tablets also contain anhydrous lactose, butylated hydroxytoluene, crospovidone, hypromellose, lactose monohydrate, and magnesium stearate as inactive ingredients.

AFINITOR DISPERZ (everolimus tablets for oral suspension) is supplied for oral administration and contains 2 mg, 3 mg, or 5 mg of everolimus. The tablets for oral suspension also contain butylated hydroxytoluene, colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, mannitol, and microcrystalline cellulose 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 mTOR complex 1 (mTORC1) and thus inhibition of mTOR kinase activity. Everolimus reduced the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic initiation factor 4E-binding protein (4E-BP1), downstream effectors of mTOR, involved in protein synthesis. S6K1 is a substrate of mTORC1 and phosphorylates the activation domain 1 of the estrogen receptor which results in ligand-independent activation of the receptor. 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.

Constitutive activation of the PI3K/Akt/mTOR pathway can contribute to endocrine resistance in breast cancer. *In vitro* studies show that estrogen-dependent and HER2+ breast cancer cells are sensitive to the inhibitory effects of everolimus, and that combination treatment with everolimus and Akt, HER2, or aromatase inhibitors enhances the anti-tumor activity of everolimus in a synergistic manner.

Two regulators of mTORC1 signaling are the oncogene suppressors tuberin-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

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 5 ng/mL, once acceptable efficacy has been achieved, additional dose increase may not be necessary.

12.3 Pharmacokinetics

Absorption

After administration of AFINITOR tablets 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 with daily dosing between 5 mg and 10 mg. With single 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.

Dose Proportionality in Patients with SEGA and TSC: In patients with SEGA and TSC, everolimus C_{min} was approximately dose-proportional within the dose range from 1.35 mg/m^2 to 14.4 mg/m^2.

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%.

In healthy subjects who received 9 mg of AFINITOR DISPERZ, high-fat meals (containing approximately 1000 calories and 55 grams of fat) reduced everolimus AUC by 12% and C_{max} by 60% and low-fat meals (containing approximately 500 calories and 20 grams of fat) reduced everolimus AUC by 30% and C_{max} by 50%.

Relative bioavailability of AFINITOR DISPERZ (everolimus tablets for oral suspension): The $AUC_{0-\infty}$ of AFINITOR DISPERZ was equivalent to that of AFINITOR Tablets; the C_{max} of this dosage form was 20%-36% lower than that of AFINITOR Tablets. The predicted trough concentrations at steady-state were similar after daily administration.

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.

Elimination

No specific elimination 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 (8.7)]*.

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 HR+ BC, advanced NET, 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 patients with SEGA and mild or moderate hepatic impairment, adjust the dose of AFINITOR Tablets or AFINITOR DISPERZ based on therapeutic drug monitoring. For patients with SEGA and severe hepatic impairment, reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ by approximately 50% and adjust subsequent doses based on therapeutic drug monitoring *[see Dosage and Administration (2.4, 2.5)]*.

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.

In patients with SEGA, the geometric mean C_{min} values normalized to mg/m^2 dose in patients aged < 10 years and 10 to 18 years were lower by 54% and 40%, respectively, than those observed in adults (> 18 years of age), suggesting that everolimus clearance normalized to body surface area was higher in pediatric patients as compared to adults.

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.

12.6 QT/QTc Prolongation Potential

In a randomized, placebo-controlled, cross-over 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.

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/m^2/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 2 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. Sperm motility, sperm count, and plasma testosterone levels were diminished in rats treated with 5 mg/kg. These doses result in exposures which are within the range of therapeutic exposure (52 ng•hr/mL and 414 ng•hr/mL respectively compared to 560 ng•hr/mL human exposure at 10 mg/day), and resulted in infertility in the rats 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 increased incidence of pre-implantation loss, suggesting that the drug may reduce female fertility.

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 Hormone Receptor-Positive, HER2-Negative Breast Cancer

A randomized, double-blind, multicenter study (BOLERO-2, NCT00863655) of AFINITOR plus exemestane versus placebo plus exemestane was conducted in 724 postmenopausal women with estrogen receptor-positive, HER2/neu-negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. Randomization was stratified by documented sensitivity to prior hormonal therapy (yes versus no) and by the presence of visceral metastasis (yes versus no). Sensitivity to prior hormonal therapy was defined as either (1) documented clinical benefit (complete response [CR], partial response [PR], stable disease ≥ 24 weeks) to at least one prior hormonal therapy in the advanced setting or (2) at least 24 months of adjuvant hormonal therapy prior to recurrence. Patients were permitted to have received 0-1 prior lines of chemotherapy for advanced disease.

The primary endpoint for the trial was progression-free survival (PFS) evaluated by Response Evaluation Criteria In Solid Tumors (RECIST), based on investigator (local radiology) assessment. Other endpoints included overall survival (OS), objective response rate (ORR), and safety.

Patients were randomly allocated in a 2:1 ratio to AFINITOR 10 mg/day plus exemestane 25 mg/day (n=485) or to placebo plus exemestane 25 mg/day (n=239). The two treatment groups were generally balanced with respect to baseline demographics and disease characteristics. Patients were not permitted to cross over to AFINITOR at the time of disease progression.

The median progression-free survival by investigator assessment at the time of the final PFS analysis was 7.8 and 3.2 months in the AFINITOR and placebo arms, respectively [HR = 0.45 (95% CI: 0.38, 0.54), one-sided log-rank p <0.0001] (see Table 14 and Figure 1). The results of the PFS analysis based on independent central radiological assessment were consistent with the investigator assessment. PFS results were also consistent across the subgroups of age, race, presence and extent of visceral metastases, and sensitivity to prior hormonal therapy.

Objective response rate was 12.6% (95% CI: 9.8, 15.9) in the AFINITOR plus exemestane arm versus 1.7% (95% CI: 0.5, 4.2) in the placebo plus exemestane arm. There were 3 complete responses (0.6%) and 58 partial responses (12.0%) in the

AFINITOR plus exemestane arm. There were no complete responses and 4 partial responses (1.7%) in the placebo plus exemestane arm.

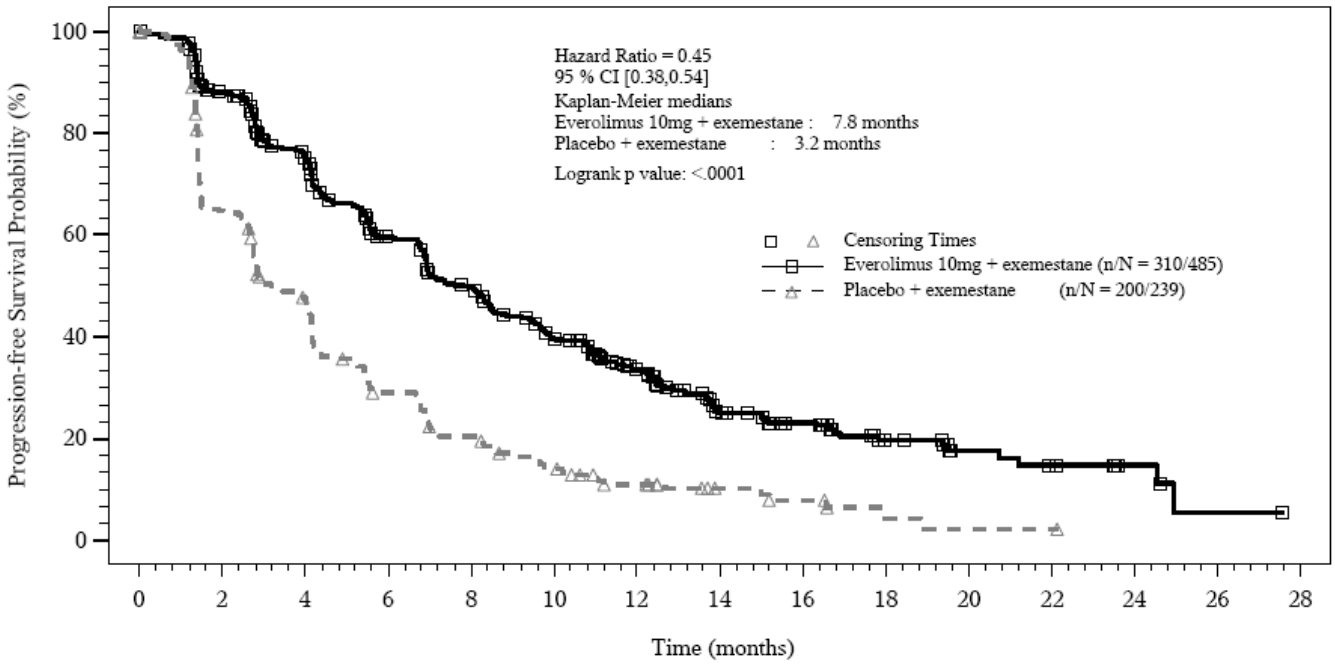
After a median follow-up of 39.3 months, there was no statistically significant difference in OS between the AFINITOR plus exemestane arm and the placebo plus exemestane arm [HR 0.89 (95% CI 0.73, 1.10)].

Table 14: Progression-free Survival Results

Analysis	AFINITOR + exemestane[a] N = 485	Placebo + exemestane[a] N = 239	Hazard ratio	P-value
Median progression-free survival (months, 95% CI)				
Investigator radiological review	7.8 (6.9 to 8.5)	3.2 (2.8 to 4.1)	0.45[b] (0.38 to 0.54)	<0.0001[c]
Independent radiological review	11.0 (9.7 to 15.0)	4.1 (2.9 to 5.6)	0.38[b] (0.3 to 0.5)	<0.0001[c]
Best overall response (%, 95% CI)				
Objective response rate (ORR)[d]	12.6% (9.8 to 15.9)	1.7% (0.5 to 4.2)	n/a[e]	

[a] Exemestane (25 mg/day)
[b] Hazard ratio is obtained from the stratified Cox proportional-hazards model by sensitivity to prior hormonal therapy and presence of visceral metastasis
[c] p-value is obtained from the one-sided log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis
[d] Objective response rate = proportion of patients with CR or PR
[e] not applicable

Figure 1: Kaplan-Meier Progression-free Survival Curves (Investigator Radiological Review)



14.2 Advanced Neuroendocrine Tumors

Locally Advanced or Metastatic Advanced Pancreatic Neuroendocrine Tumors (PNET)

A randomized, double-blind, multi-center trial (RADIANT-3, NCT00510068) 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 versus no) and by WHO performance status (0 versus 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 10 mg/day (n=207) or placebo (n=203). Demographics were well balanced (median age 58 years, 55% male, 79% Caucasian). Of the 203 patients randomized to best supportive care, 172 patients (85%) received AFINITOR following documented radiologic progression.

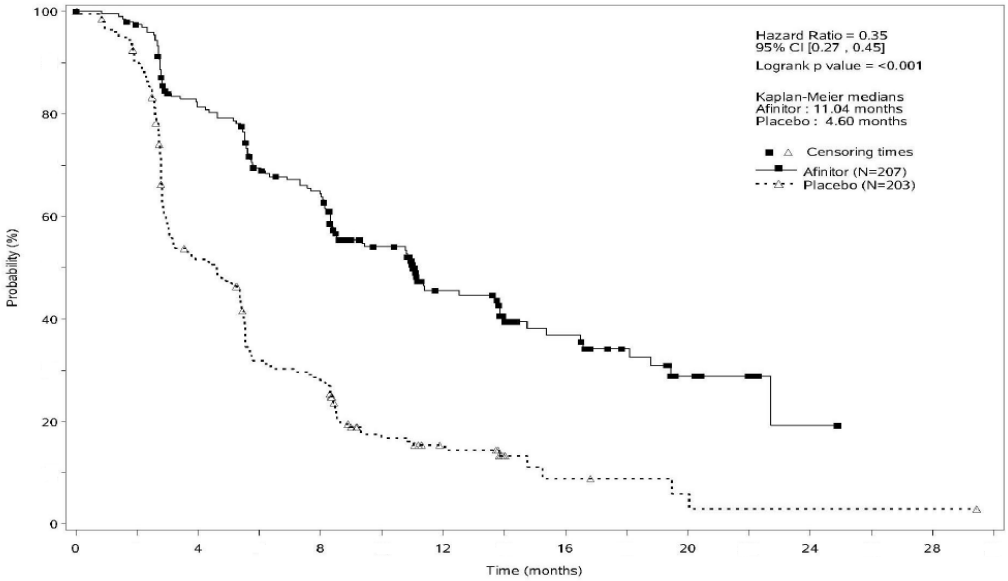
The trial demonstrated a statistically significant improvement in PFS (median 11.0 months versus 4.6 months), resulting in a 65% risk reduction in investigator-determined PFS (HR 0.35; 95%CI: 0.27 to 0.45; p<0.001) (see Table 15 and Figure 2). PFS improvement was observed across all patient subgroups, 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 15.

Table 15: 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 2: Kaplan-Meier Investigator-Determined Progression-free Survival Curves



Investigator-determined response rate was 4.8% in the AFINITOR arm and there were no complete responses. Overall survival was not statistically significantly different between study arms [HR=0.94 (95% CI 0.73 to 1.20); p=0.30].

Unresectable, Locally Advanced or Metastatic, Well-Differentiated, Non-Functional Neuroendocrine Tumors of Gastrointestinal or Lung Origin

A randomized, double-blind, multicenter study (RADIANT-4, NCT01524783) of AFINITOR plus best supportive care (BSC) versus placebo plus best supportive care was conducted in patients with unresectable, locally advanced or

metastatic, well differentiated, non-functional neuroendocrine tumors (NET) of gastrointestinal (excluding pancreatic) or lung origin. The study required that patients had well-differentiated (low or intermediate grade) histology, no prior or current history of carcinoid symptoms, and evidence of disease progression within 6 months prior to randomization. Patients were randomized 2:1 to receive either AFINITOR 10 mg/day or placebo, and stratified by prior somatostatin analog (SSA) use (yes versus no), tumor origin and WHO performance status (0 versus 1).

The major efficacy outcome measure was progression-free survival (PFS) based on independent radiological assessment evaluated by RECIST. Additional efficacy outcome measures were overall survival and overall response rate. A total of 302 patients were randomized, 205 to the AFINITOR arm and 97 to the placebo arm. The median age was 63 years (range 22 to 86); 47% were male; 76% were White; 74% had WHO performance status (PS) 0 and 26% had WHO PS 1. The most common primary sites of tumor were lung (30%), ileum (24%), and rectum (13%).

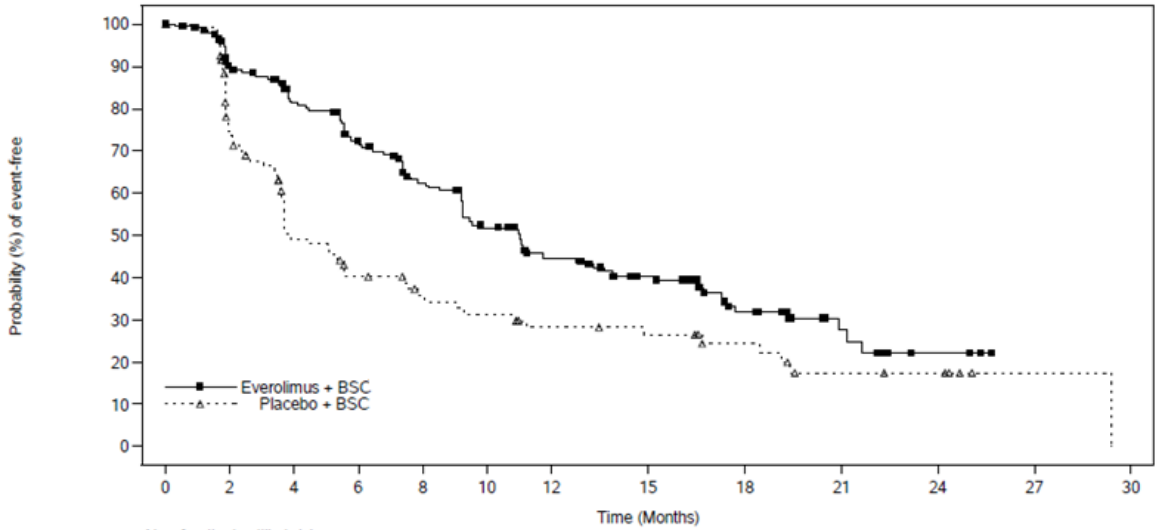
The study demonstrated a statistically significant improvement in PFS per independent radiological review (see Table 16 and Figure 3). There was no statistically significant difference in OS at the planned interim analysis.

Table 16: Efficacy Results

	AFINITOR N=205	**Placebo N=97**
Progression-Free Survival		
Number of Events	113 (55%)	65 (67%)
Progressive Disease	104 (51%)	60 (62%)
Death	9 (4%)	5 (5%)
Median PFS in months (95% CI)	11.0 (9.2, 13.3)	3.9 (3.6, 7.4)
Hazard Ratio (95%CI)[1]	0.48 (0.35, 0.67)	
p-value[2]	<0.001	
Overall Response Rate	2%	1%

1. Hazard ratio is obtained from the stratified Cox model.
2. p-value is obtained from the stratified log-rank test.

Figure 3: Kaplan-Meier Progression-free Survival Curves



No.of patients still at risk

Time (Months)	0	2	4	6	8	10	12	15	18	21	24	27	30
Everolimus + BSC	205	168	145	124	101	81	65	52	26	10	3	0	0
Placebo + BSC	97	65	39	30	24	21	17	15	11	6	5	1	0

Lack of Efficacy in Locally Advanced or Metastatic Functional Carcinoid Tumors

The safety and effectiveness of AFINITOR in patients with locally advanced or metastatic functional carcinoid tumors have not been demonstrated. In a randomized (1:1), double-blind, multi-center trial (RADIANT-2, NCT00412061) in 429 patients with carcinoid tumors, AFINITOR plus depot octreotide (Sandostatin LAR®) was compared to placebo plus depot octreotide. After documented radiological progression, patients on the placebo arm could receive AFINITOR; of those randomized to placebo, 143 (67%) patients received open-label AFINITOR plus depot octreotide. The study did not meet

its primary efficacy endpoint of a statistically significant improvement in PFS and the final analysis of OS favored the placebo plus depot octreotide arm.

14.3 Advanced Renal Cell Carcinoma

An international, multi-center, randomized, double-blind trial (RECORD-1, NCT00410124) 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[1] and prior anticancer therapy.

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 2 arms (median age 61 years; 77% male, 88% Caucasian, 74% received prior sunitinib or sorafenib, and 26% received both sequentially).

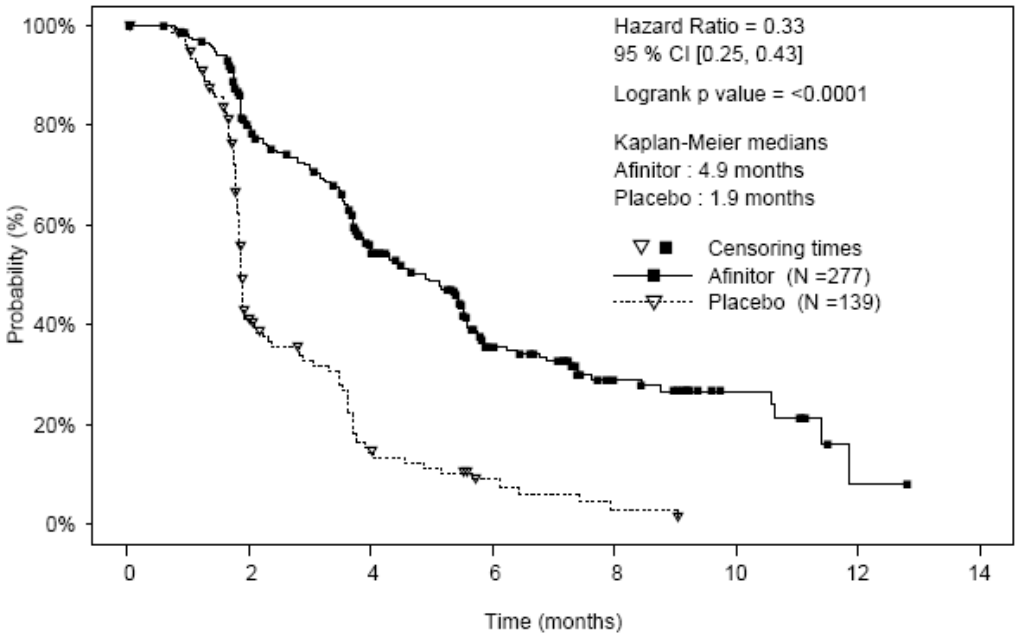
AFINITOR was superior to placebo for PFS (see Table 17 and Figure 4). The treatment effect was similar across prognostic scores and prior sorafenib and/or sunitinib. Final overall survival (OS) results yield a hazard ratio of 0.90 (95% CI: 0.71 to 1.14), with no statistically significant difference between the 2 treatment groups. Planned cross-over 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 17: 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 4: Kaplan-Meier Progression-free Survival Curves



14.4 Renal Angiomyolipoma with Tuberous Sclerosis Complex

A randomized (2:1), double-blind, placebo-controlled trial (EXIST-2, NCT00790400) of AFINITOR was conducted in 118 patients with renal angiomyolipoma as a feature of TSC (n=113) or sporadic lymphangioleiomyomatosis (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 ≥ 50% reduction in angiomyolipoma volume, absence of new angiomyolipoma lesion ≥ 1 cm, absence of kidney volume increase ≥ 20%, and no angiomyolipoma related bleeding of ≥ Grade 2. Key supportive efficacy outcome measures were time to angiomyolipoma progression and skin lesion response rate. The primary analyses of efficacy outcome measures were limited to the blinded treatment period and conducted 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 versus 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 1 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 cm^3 (range 9 to 1612 cm^3) and 120 cm^3 (range 3 to 4520 cm^3) 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) at the time of the primary analysis.

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 18. The median response duration was 5.3+ months (range 2.3+ to 19.6+ months).

There were 3 patients in the AFINITOR arm and 8 patients in the placebo arm with documented angiomyolipoma progression by central radiologic review (defined as a ≥ 25% increase from nadir in the sum of angiomyolipoma target lesion volumes to a value greater than baseline, appearance of a new angiomyolipoma ≥ 1.0 cm in longest diameter, an increase in renal volume ≥ 20% from nadir for either kidney and to a value greater than baseline, or Grade ≥ 2 angiomyolipoma-related bleeding). 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).

Table 18: 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

Skin lesion response rates were assessed by local investigators for 77 patients in the AFINITOR arm and 37 patients in the placebo arm who presented with skin lesions at study entry. The skin lesion response rate was statistically significantly higher in the AFINITOR arm (26% versus 0, p=0.0011); all skin lesion responses were partial responses, defined as visual improvement in 50%-99% of all skin lesions durable for at least 8 weeks (Physician's Global Assessment of Clinical Condition).

Patients randomized to placebo were permitted to receive AFINITOR at the time of angiomyolipoma progression or after the time of the primary analysis. After the primary analysis, patients treated with AFINITOR underwent additional follow-up CT or MRI scans to assess tumor status until discontinuation of treatment or completion of 4 years of follow-up after the last patient was randomized. A total of 112 patients (79 randomized to AFINITOR and 33 randomized to placebo) received at least one dose of AFINITOR. The median duration of AFINITOR treatment was 3.9 years (range: 0.5 months to 5.3 years) and the median duration of follow-up was 3.9 years (range: 0.9 months to 5.4 years). During the follow-up period after the primary analysis, 32 patients (in addition to the 33 patients identified at the time of the primary analysis) had an angiomyolipoma response based upon independent central radiology review. Among the 65 responders out of 112 patients, the median time to angiomyolipoma response was 2.9 months (range: 2.6 to 33.8 months). Sixteen of the 112 patients treated with AFINITOR had angiomyolipoma progression by the end of the follow-up period. No patient underwent a nephrectomy for angiomyolipoma progression and one patient underwent renal embolization while treated with AFINITOR.

14.5 Subependymal Giant Cell Astrocytoma with Tuberous Sclerosis Complex

A randomized (2:1), double-blind, placebo-controlled trial (EXIST-1, NCT00789828) of AFINITOR was conducted in 117 pediatric and adult patients with subependymal giant cell astrocytoma (SEGA) and tuberous sclerosis complex (TSC). Eligible patients had at least one SEGA lesion ≥ 1.0 cm in longest diameter on MRI based on local radiology assessment and one or more of the following: serial radiological evidence of SEGA growth, a new SEGA lesion ≥ 1 cm in longest diameter, or new or worsening hydrocephalus. Patients randomized to the treatment arm received AFINITOR tablets at a starting dose of 4.5 mg/m^2 daily, with subsequent dose adjustments as needed to achieve and maintain everolimus trough concentrations of 5 to 15 ng/mL as tolerated. AFINITOR/matched placebo treatment continued until disease progression or unacceptable toxicity. MRI scans for disease assessment were obtained at baseline, 12, 24, and 48 weeks, and annually thereafter.

The main efficacy outcome measure was SEGA response rate based on independent central radiology review. SEGA response was defined as a ≥ 50% reduction in the sum of SEGA volume relative to baseline, in the absence of unequivocal worsening of non-target SEGA lesions, a new SEGA lesion ≥ 1 cm, and new or worsening hydrocephalus. The primary analysis of SEGA response rate was limited to the blinded treatment period and conducted 6 months after the last patient was randomized. The analysis of SEGA response rate was stratified by use of enzyme-inducing antiepileptic drugs (EIAEDs) at randomization (yes versus no).

Of the 117 patients enrolled, 78 were randomized to AFINITOR and 39 to placebo. The median age was 9.5 years (range 0.8 to 26 years; 69% were 3 to < 18 years at enrollment; 17% were < 3 years at enrollment), 57% were male, and 93% were Caucasian. At baseline, 18% of patients were receiving EIAEDs. Based on central radiology review at baseline, 98% of patients had at least one SEGA lesion ≥ 1.0 cm in longest diameter, 79% had bilateral SEGAs, 43% had ≥ 2 target SEGA lesions, 26% had growth in or into the inferior surface of the ventricle, 9% had evidence of growth beyond the subependymal tissue adjacent to the ventricle, and 7% had radiographic evidence of hydrocephalus. The median values for the sum of all target SEGA lesions at baseline were 1.63 cm^3 (range 0.18 to 25.15 cm^3) and 1.30 cm^3 (range 0.32 to 9.75 cm^3) in the AFINITOR and placebo arms respectively. Eight (7%) patients had prior SEGA-related surgery. The median duration of follow-up was 8.4 months (range 4.6 to 17.2 months) at the time of primary analysis.

The SEGA response rate was statistically significantly higher in AFINITOR-treated patients. There were 27 (35%) patients with SEGA responses in the AFINITOR arm and no SEGA responses in the placebo arm. Results are displayed in

Table 19. At the time of the primary analysis, all SEGA responses were ongoing and the median duration of response was 5.3 months (range 2.1 to 8.4 months).

With a median follow-up of 8.4 months, SEGA progression was detected in 6 of 39 (15.4%) patients randomized to receive placebo and none of the 78 patients randomized to receive AFINITOR. No patient in either treatment arm required surgical intervention.

Table 19: SEGA Response

	AFINITOR N=78	**Placebo N=39**	**p-value**
Primary analysis			
SEGA response rate[a] - (%)	**35**	**0**	**<0.0001**
95% CI	24, 46	0, 9	

[a] Per independent central radiology review

Patients randomized to placebo were permitted to receive AFINITOR at the time of SEGA progression or after the primary analysis, whichever occurred first. After the primary analysis, patients treated with AFINITOR underwent additional follow-up MRI scans to assess tumor status until discontinuation of treatment or completion of 4 years of follow-up after the last patient was randomized. A total of 111 patients (78 patients randomized to AFINITOR and 33 patients randomized to placebo) received at least one dose of AFINITOR. Median duration of AFINITOR treatment and follow-up was 3.9 years (range: 0.2 to 4.9 years).

By four years after the last patient was enrolled, a total of 64 of the 111 patients treated with AFINITOR had a ≥ 50% reduction in SEGA volume relative to baseline, including 27 patients identified at the time of the primary analysis and 37 patients with a SEGA response after the primary analysis. The median time to SEGA response was 5.3 months (range: 2.5 to 33.1 months). Thirteen of the 111 patients treated with AFINITOR had documented disease progression by the end of the follow-up period and no patient required surgical intervention for SEGA during the course of the study.

Study 2485 (NCT NCT00411619) was an open-label, single-arm trial conducted to evaluate the safety and antitumor activity of AFINITOR 3.0 mg/m^2/orally once daily in patients with SEGA and TSC. Serial radiological evidence of SEGA growth was required for entry. Tumor assessments were performed every 6 months for 60 months after the last patient was enrolled or disease progression, whichever occurred earlier. The major efficacy outcome measure was the reduction in volume of the largest SEGA lesion with 6 months of treatment, as assessed via independent central radiology review. Progression was defined as an increase in volume of the largest SEGA lesion over baseline that was ≥ 25% over the nadir observed on study.

Study 2485 enrolled 28 patients who received AFINITOR for a median duration of 5.7 years (range: 5 months to 6.9 years); 23 of 28 patients (82%) remained on AFINITOR for at least 5 years. Across the study population, the median age was 11 years (range 3-34), 61% male, 86% Caucasian.

At the primary analysis, 9 of 28 patients [32% (95% CI: 16% to 52%)] had an objective response at 6 months, defined as at least a 50% decrease in volume of the largest SEGA lesion. At the completion of the study, the median duration of durable response was 12 months (range 3 months to 6.3 years).

By 60 months after the last patient was enrolled, 11% of patients (3/28) had documented disease progression. No patient developed a new SEGA lesion while on AFINITOR. Nine additional patients were identified as having a ≥50% volumetric reduction in their largest SEGA lesion between 1 to 4 years after initiating AFINITOR including 3 patients who had surgical resection with subsequent regrowth prior to receiving AFINITOR.

15 REFERENCES

1. 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.
2. OSHA Hazardous Drugs. *OSHA*. http://www.osha.gov/SLTC/hazardousdrugs/index.html.

16 HOW SUPPLIED/STORAGE AND HANDLING

AFINITOR (everolimus) Tablets

2.5 mg tablets
White to slightly yellow, elongated tablets with a bevelled edge and 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 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 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 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

AFINITOR DISPERZ (everolimus tablets for oral suspension)

2 mg tablets for oral suspension
White to slightly yellowish, round, flat tablets with a bevelled edge and engraved with "D2" on one side and "NVR" on the other; available in:
Blisters of 28 tablets.....NDC 0078-0626-51
Each carton contains 4 blister cards of 7 tablets each

3 mg tablets for oral suspension
White to slightly yellowish, round, flat tablets with a bevelled edge and engraved with "D3" on one side and "NVR" on the other; available in:
Blisters of 28 tablets.....NDC 0078-0627-51
Each carton contains 4 blister cards of 7 tablets each

5 mg tablets for oral suspension
White to slightly yellowish, round, flat tablets with a bevelled edge and engraved with "D5" on one side and "NVR" on the other; available in:
Blisters of 28 tablets.....NDC 0078-0628-51
Each carton contains 4 blister cards of 7 tablets each

Store AFINITOR (everolimus) Tablets and AFINITOR DISPERZ (everolimus tablets for oral suspension) at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 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.

Follow special handling and disposal procedures for anticancer pharmaceuticals.[2]

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

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)]*.

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 sepsis, 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)]*.

Angioedema with Concomitant use of Angiotensin-Converting Enzyme (ACE) Inhibitors

Inform patients that they are more susceptible to angioedema if concomitantly taking angiotensin-converting enzyme (ACE) inhibitors. Patients should be aware of any signs or symptoms of angioedema and seek prompt medical attention *[see Warnings and Precautions (5.3)]*.

Stomatitis

Inform patients of the possibility of developing stomatitis. In such cases, mouthwashes and/or other topical treatments are recommended, but these should not contain alcohol, peroxide, iodine, or thyme *[see Dosage and Administration (2.2) and Warnings and Precautions (5.4)]*.

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 (5.5)]*.

Impaired Wound Healing

Inform patients of the possibility of impaired wound healing or dehiscence while being treated with AFINITOR *[see Warnings and Precautions (5.6)]*.

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 (5.8)]*.

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/PgP inhibitors or inducers while on AFINITOR treatment *[see Dosage and Administration (2.2, 2.5), Warnings and Precautions (5.9), and Drug Interactions (7.1, 7.2)]*.

Vaccinations

Advise patients to avoid the use of live vaccines and close contact with those who have received live vaccines *[see Warnings and Precautions (5.11)]*.

Embryo-Fetal Toxicity

AFINITOR can cause fetal harm if taken during pregnancy. Advise a pregnant woman of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 8 weeks after the last dose of AFINITOR. Advise patients to inform their healthcare provider of a known or suspected pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 4 weeks after the last dose of AFINITOR *[see Warnings and Precautions (5.12) and Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise women that breastfeeding is not recommended during treatment with AFINITOR and for 2 weeks after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males and females of reproductive potential of the potential risk for impaired fertility *[see Use in Specific Populations (8.3)]*.

Safe Handling Practices for AFINITOR DISPERZ

Advise patients and their caregivers to read and carefully follow the FDA approved AFINITOR DISPERZ "Instructions for Use".

Dosing Instructions

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

Inform patients to take AFINITOR DISPERZ orally once daily at the same time every day as a suspension. Refer patients to the "Instructions for Use" pamphlet for additional information regarding these procedures.

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.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T201X-XX
September 2017

PATIENT INFORMATION

AFINITOR® (a-fin-it-or) (everolimus) tablets	**AFINITOR® DISPERZ (a-fin-it-or dis-perz) (everolimus tablets for oral suspension)**

Read this Patient Information leaflet that comes with AFINITOR or AFINITOR DISPERZ 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 and AFINITOR DISPERZ?

AFINITOR and AFINITOR DISPERZ 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
   - Chills
   - Skin rash
   - Joint pain and inflammation
   - Tiredness
   - Loss of appetite
   - Nausea
   - Pale stools or dark urine
   - Yellowing of the skin
   - Pain in the upper right side of the stomach
3. **Possible increased risk for a type of allergic reaction called angioedema**, in people who take an Angiotensin-Converting Enzyme (ACE) inhibitor medicine during treatment with AFINITOR or AFINITOR DISPERZ. Talk with your healthcare provider before taking AFINITOR or AFINITOR DISPERZ if you are not sure if you take an ACE inhibitor medicine. Get medical help right away if you have trouble breathing or develop swelling of your tongue, mouth, or throat during treatment with AFINITOR.
4. **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 or AFINITOR DISPERZ.

If you have any of the serious side effects listed above, you may need to stop taking AFINITOR or AFINITOR DISPERZ 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:

- advanced hormone receptor-positive, HER2-negative breast cancer, along with the medicine exemestane, in postmenopausal women who have already received certain other medicines for their cancer.
- adults with a type of pancreatic cancer known as pancreatic neuroendocrine tumor (PNET), that has progressed and cannot be treated with surgery.
- adults with a type of cancer known as neuroendocrine tumor (NET) of the stomach and intestine (gastrointestinal), or lung that has progressed and cannot be treated with surgery.

  AFINITOR is not for use in people with carcinoid tumors that actively produce hormones.
- adults 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):
  - adults with a kidney tumor called angiomyolipoma, when their kidney tumor does not require surgery right away.
  - adults and children with a brain tumor called subependymal giant cell astrocytoma (SEGA) when the tumor cannot be removed completely by surgery.

What is AFINITOR DISPERZ?

AFINITOR DISPERZ is a prescription medicine used to treat:

- adults and children with a genetic condition called tuberous sclerosis complex (TSC) who have a brain tumor called subependymal giant cell astrocytoma (SEGA) when the tumor cannot be removed completely by surgery.

Who should not take AFINITOR or AFINITOR DISPERZ?

Do not take AFINITOR or AFINITOR DISPERZ if you are allergic to everolimus or to any of the ingredients in AFINITOR or AFINITOR DISPERZ. See the end of this leaflet for a complete list of ingredients in AFINITOR and AFINITOR DISPERZ.

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 or AFINITOR DISPERZ?

Before taking AFINITOR or AFINITOR DISPERZ, 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 or AFINITOR DISPERZ. If you are not sure about the type of immunization or vaccine, ask your healthcare provider.
- Are pregnant, could become pregnant, or have a partner who could become pregnant. AFINITOR or AFINITOR DISPERZ can cause harm to your unborn baby. If you are a woman who is able to become pregnant you should use effective birth control during treatment and for 8 weeks after your last dose of AFINITOR or AFINITOR DISPERZ. If you are a man with a woman partner, you should use effective birth control during treatment and for 4 weeks after your last dose of AFINITOR or AFINITOR DISPERZ. Talk to your healthcare provider about birth control methods that may be right for you during this time. If you become pregnant or think you are pregnant, tell your healthcare provider right away.
- Are breastfeeding or plan to breastfeed. It is not known if AFINITOR or AFINITOR DISPERZ passes into your breast milk. Do not breastfeed during treatment and for 2 weeks after your last dose of AFINITOR or AFINITOR DISPERZ.
- Are about to have surgery, if you have had a recent surgery, or if you have an unhealed wound

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

AFINITOR or AFINITOR DISPERZ may affect the way other medicines work, and other medicines can affect how AFINITOR or AFINITOR DISPERZ work. Taking AFINITOR or AFINITOR DISPERZ 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 weaken your immune system (your body’s ability to fight infections and other problems)

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 or AFINITOR DISPERZ may need to be changed. You should also tell your healthcare provider before you start taking any new medicine.

How should I take AFINITOR or AFINITOR DISPERZ?

- Your healthcare provider will prescribe the dose of AFINITOR or AFINITOR DISPERZ that is right for you.
- Take AFINITOR or AFINITOR DISPERZ exactly as your healthcare provider tells you to.
- When you start treatment with AFINITOR, your healthcare provider may also prescribe a mouthwash to reduce the likelihood of getting mouth ulcers or sores and to reduce their severity. Follow your healthcare provider's instructions on how to use this prescription mouthwash.
- Your healthcare provider may change your dose of AFINITOR or AFINITOR DISPERZ or tell you to temporarily interrupt dosing, if needed.
- **Take only AFINITOR or AFINITOR DISPERZ. Do not mix AFINITOR and AFINITOR DISPERZ together.**
- Use scissors to open the blister pack.

AFINITOR:

- Swallow AFINITOR tablets whole with a glass of water. Do not take any tablet that is broken or crushed.

AFINITOR DISPERZ:

- If your healthcare provider prescribes AFINITOR DISPERZ for you, see the "Instructions for Use" that come with your medicine for instructions on how to prepare and take your dose.
- Each dose of AFINITOR DISPERZ must be prepared as a suspension before it is given.
- AFINITOR DISPERZ can cause harm to an unborn baby. When possible, the suspension should be prepared by an adult who is not pregnant or planning to become pregnant.
- Wear gloves to avoid possible contact with everolimus when preparing suspensions of AFINITOR DISPERZ for another person.
- Take AFINITOR or AFINITOR DISPERZ 1 time each day at about the same time.
- Take AFINITOR or AFINITOR DISPERZ the same way each time, either with food or without food.
- If you take too much AFINITOR or AFINITOR DISPERZ contact your healthcare provider or go to the nearest hospital emergency room right away. Take the pack of AFINITOR or AFINITOR DISPERZ with you.
- If you miss a dose of AFINITOR or AFINITOR DISPERZ, 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 or AFINITOR DISPERZ, skip the dose for that day. The next day, take AFINITOR or AFINITOR DISPERZ at your usual time. Do not take 2 doses to make up for a missed dose. If you are not sure about what to do, call your healthcare provider.
- You should have blood tests before you start AFINITOR or AFINITOR DISPERZ 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 or AFINITOR DISPERZ to treat SEGA, you will also need to have blood tests regularly to measure how much medicine is in your blood. This will help your healthcare provider decide how much AFINITOR or AFINITOR DISPERZ you need to take.

What should I avoid while taking AFINITOR or AFINITOR DISPERZ?

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

What are the possible side effects of AFINITOR or AFINITOR DISPERZ?

AFINITOR and AFINITOR DISPERZ can cause serious side effects.

- **See "What is the most important information I should know about AFINITOR and AFINITOR DISPERZ?" for more information.**
- **Delayed wound healing**. AFINITOR can cause incisions to heal slowly or not heal well. Call your healthcare provider right away if you have any of the following symptoms:
  - your incision is red, warm or painful
  - blood, fluid, or pus in your incision
  - your incision opens up
  - swelling of your incision

Common side effects of AFINITOR in people with advanced hormone receptor-positive, HER2-negative breast cancer, advanced neuroendocrine tumors of the pancreas, stomach and intestine (gastrointestinal) or lung, and advanced kidney cancer include

- Mouth ulcers. AFINITOR can cause mouth ulcers and sores. When you start treatment with AFINITOR, your healthcare provider may tell you to also start a prescription mouthwash to reduce the likelihood of getting mouth ulcers or sores and to reduce their severity. Follow your healthcare provider's instructions on how to use this prescription mouthwash. If you develop pain, discomfort, or open sores in your mouth, tell your healthcare provider. Your healthcare provider may tell you to re-start this mouthwash or to use a special mouthwash or mouth gel that does not contain alcohol, peroxide, iodine, or thyme.

- Infections
- Feeling weak or tired
- Cough, shortness of breath
- Diarrhea and constipation
- Rash, dry skin, and itching
- Nausea and vomiting
- Fever
- Loss of appetite, weight loss
- Swelling of arms, hands, feet, ankles, face or other parts of the body
- Abnormal taste
- Dry mouth
- Inflammation of lining of the digestive system
- Headache
- Nose bleeds
- Pain in arms and legs, mouth and throat, back or joints
- High blood glucose
- High blood pressure
- Difficulty sleeping
- Hair loss
- Muscle spasms
- Feeling dizzy
- Nail disorders

Common side effects of AFINITOR and AFINITOR DISPERZ in people who have SEGA or renal angiomyolipoma with TSC include:

- Mouth ulcers. AFINITOR can cause mouth ulcers and sores. When you start treatment with AFINITOR, your healthcare provider may tell you to also start a prescription mouthwash to reduce the likelihood of getting mouth ulcers or sores and to reduce their severity. Follow your healthcare provider's instructions on how to use this prescription mouthwash. If you develop pain, discomfort, or open sores in your mouth, tell your healthcare provider. Your healthcare provider may tell you to re-start this mouthwash or to use a special mouthwash or mouth gel that does not contain alcohol, peroxide, iodine, or thyme.
- Infections
- Nausea and vomiting
- Diarrhea and constipation
- Swelling of your hands, arms, legs, and feet
- Joint pain
- Cough
- Skin problems (such as rash, acne, or dry skin)
- Fever
- Feeling tired
- Anxiety, aggression, and other abnormal behaviors
- Low red blood cells, white blood cells or platelets
- Increased blood cholesterol level and certain other blood tests
- Increased blood sugar levels
- Decreased blood phosphate levels

Other side effects that may occur with AFINITOR and AFINITOR DISPERZ:

- Absence of menstrual periods (menstruation). You may miss 1 or more menstrual periods. Tell your healthcare provider if this happens.
- AFINITOR and AFINITOR DISPERZ may affect fertility in females and may affect your ability to become pregnant. Talk to your healthcare provider if this is a concern for you.
- AFINITOR and AFINITOR DISPERZ may affect fertility in males and may affect your ability to father a child. Talk to your healthcare provider if this is a concern for you.

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 and AFINITOR DISPERZ. 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 should I store AFINITOR or AFINITOR DISPERZ?

- Store AFINITOR or AFINITOR DISPERZ at room temperature, between 68°F to 77°F (20°C to 25°C).
- Keep AFINITOR or AFINITOR DISPERZ in the pack it comes in.
- Open the blister pack just before taking AFINITOR or AFINITOR DISPERZ.
- Keep AFINITOR or AFINITOR DISPERZ dry and away from light.
- Do not use AFINITOR or AFINITOR DISPERZ that is out of date or no longer needed.

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

General information about AFINITOR and AFINITOR DISPERZ

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use AFINITOR or AFINITOR DISPERZ for a condition for which it was not prescribed. Do not give AFINITOR or AFINITOR DISPERZ 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 and AFINITOR DISPERZ. 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: anhydrous lactose, butylated hydroxytoluene, crospovidone, hypromellose, lactose monohydrate, and magnesium stearate.

What are the ingredients in AFINITOR DISPERZ?

Active ingredient: everolimus.

Inactive ingredients: butylated hydroxytoluene, colloidal silicon dioxide, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, mannitol, and microcrystalline cellulose.

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T201X-XX/T201X-XX

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 9/2017