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 ($AUC_{0\text{-}24h}$) 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.

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.

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